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CUK-H06402-45- P25309

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The *British Journal of Surgery* ISSN 0007-1323

Published on behalf of the British Journal of Surgery Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
Joint Editors, *British Journal of Surgery*, Blackwell Science Ltd,
25 John Street, London WC1N 2BL, UK (Tel: +44 171 404 1831).

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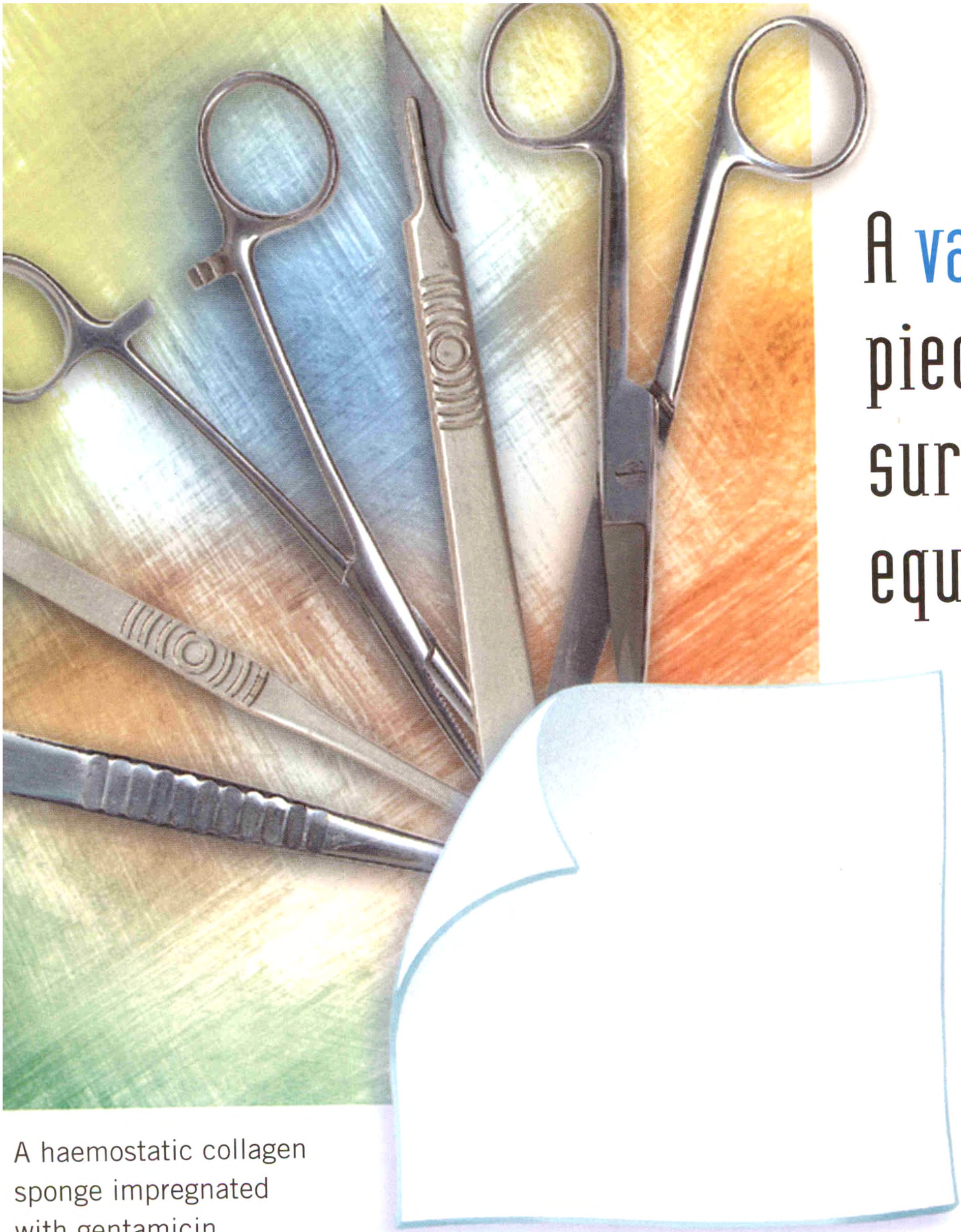

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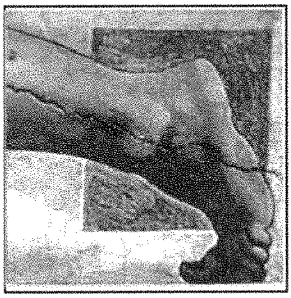

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Outcome measures after lower extremity bypass surgery: there is more than just patency

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Arterial occlusive disease is a generalized, progressive, and disabling condition that can significantly influence the quality of a patient's life. When it affects peripheral vessels this chronic disease may cause considerable morbidity, particularly when it progresses to gangrene. At other sites it is responsible for an increased mortality from myocardial infarction and stroke.

To improve some of this unfavourable outlook lower extremity bypass surgery down to the level of the ankle and foot has been recommended, even in elderly patients with extensive disease. Such procedures, however, are associated with a high failure rate leading to further surgical interventions and hospital stays. The traditionally reported outcomes of bypass operations are graft patency, limb salvage and patient survival[1], but these indicators of surgical success are limited as measurements of outcome because they do not tell the whole story from the patient's perspective. All vascular surgeons know that major amputation may sometimes be necessary in spite of graft patency, and that graft occlusion is not always associated with a reduction in quality of life.

For a proper appreciation of the situation many factors must be considered, particularly delayed wound healing, residual postoperative pain and leg swelling, episodes of recurrent ischaemia, number of reoperations, maintenance of ambulation and residential status, opposite leg problems and cardiovascular events. Moreover, increasing emphasis has been placed in recent years on assessment of perception of well being, functional capacity and life quality[2]. Nicoloff *et al.*[3] found that only 14 per cent of patients who had limb salvage surgery achieved the ideal result of an uncomplicated operation with long-term symptom relief, preservation of functional status, and no recurrence or repeat operations. This disappointing picture occurred in spite of an excellent assisted primary graft patency rate of 77 per cent and a limb salvage rate of no less than 87 per cent at 5 years.

To allow a more comprehensive view of the effectiveness of bypass surgery, including its impact on daily life and life satisfaction, outcome measurements of vascular interventions must reflect a more complete array of endpoints than those commonly applied. An important issue in the effectiveness of vascular surgery is the need for repeat operative intervention. From recent studies it is evident that many patients who had bypass surgery for limb salvage require ongoing reoperations for persistent or recurrent symptoms until their death, implying significant morbidity, discomfort, and additional costs[3,4]. We believe that additional interventions for a graft-related complication, recurrent leg ischaemia or delayed wound healing should be used as a principal outcome measure in clinical studies.

It is also recognized that over time many patients treated for ischaemic symptoms in one leg will return with similar symptoms in the opposite leg[5]. The risk that symptoms will develop in the contralateral limb varies from 8 to 21 per cent per annum and emphasizes that peripheral arterial occlusive disease is essentially a two-limb problem. This information is important for patients, in particular for those with contralateral claudication, and should be discussed in full when considering surgery. Since atherosclerotic disease is generalized, outcome studies that include non-fatal major vascular events are important[6,7]. Moreover, as first-event mortality from stroke and myocardial infarction has declined, the number of non-fatal vascular events has increased, leaving a majority of survivors with residual emotional, social and/or physical impairments that adversely affect their quality of life.

A major outcome measure in understanding patient well being is the duration and intensity of rehabilitation after intervention. In assessing functional status, well being and symptom relief after bypass surgery for severe leg ischaemia, Gibbons *et al.*[8] underlined the fact that less than 50 per cent of patients report feeling 'back to normal' at 6 months. Leg swelling in particular, often persisting beyond 6 months after operation, deserves our attention in future studies to seek remedies for its improvement. Another relevant endpoint after revascularization of threatened limbs is the preservation of independent living and ambulation, at different time intervals from the intervention, in order to identify trends in social and physical functioning. One study found that at 6 months after bypass surgery independent living and ambulation were maintained in 99 and 97 per cent of patients respectively[9]. When limb loss occurred, 73 per cent of the surviving amputees were living at home and 81 per cent were walking independently 1 year after amputation[10]. With few exceptions, such information is lacking in the available literature. In summary, many additional indicators of morbidity can and should be used to evaluate the impact of vascular surgery; these should serve as direct measures of effectiveness, alongside patency.

The need to assess subjective aspects of health-related quality of life after vascular surgery is becoming ever more recognized[2]. Patient-valued outcomes, including functional ability, life satisfaction and expectation regarding longevity of the vascular intervention, should also be measured. Generic health status questionnaires, such as the Short-Form 36 or Nottingham Health Profile, are available for use, but these instruments are complicated by the frequent presence of other chronic conditions in vascular patients, making it difficult to evaluate the independent effect of leg ischaemia or its treatment on overall health status[9,11]. To overcome this limitation, specifically developed instruments are required that contain questionnaire items relevant to the problems of peripheral arterial occlusive disease. Investigators have developed a validated disease-specific instrument for intermittent claudication (Walking Impairment Questionnaire), but a specific questionnaire for the measurement of health-related quality of life in those with limb-threatening ischaemia is still not available[9].

Efforts to improve the evaluation of both clinical outcome and patient satisfaction must continue. Future research in vascular surgery should include additional clinical and quality-of-life outcome measures besides patency, limb salvage and patient survival. This is important to ensure that gains in one area do not occur at the expense of others. Such information is essential in determining which treatment strategy should be abandoned and which should be accepted as best practice in the future.

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A hernia sac cannot be found at operation

During an attempt to repair an inguinal hernia difficulty is encountered in finding the sac. How should such a situation be handled? Mr Kenneth Waters of London replies.

Hernia repair is the most common general surgical operation performed[1]. Although it is often considered to be a 'minor' procedure that is straightforward to carry out, patients and hernias can vary considerably. Hernia repair may present a true clinical dilemma for both the trainee and the well-trained, not least when an inguinal canal is opened and no hernia sac is seen. In this event, one of three possibilities has occurred: the hernia sac is obscured within the inguinal canal, or the sac is outside the inguinal canal, or the swelling is not a hernia sac at all.

First, the spermatic cord should be mobilized to the deep inguinal ring margins, identifying the inferior epigastric vessels; then it should be searched carefully for an indirect hernia. A thickened cremasteric fascia can obscure an underlying thin sac and this fascia should therefore be divided along the length of the cord, taking care to preserve the vas deferens and cord vessels. When the deep ring margins are reached, the cremasteric fascia and associated cremaster muscle may be detached transversely. A small sac not seen lower down may then become visible just below the deep ring orifice. This should not be confused with the normal small peritoneal prolongation.

The cord may contain lipomas which are of preperitoneal origin and so are themselves true hernias[2]. They may, however, obscure a peritoneal sac or completely encircle it. The fascia overlying each lipoma should be opened and the fatty tissue teased out. A peritoneal sac may then be revealed. If a swelling is present that is not obviously a lipoma, it may be a sliding hernia of colon with little or no evidence of a sac. This should be treated carefully, not opened but mobilized gently towards the deep ring with blunt dissection when a small peritoneal sac will often be found anteriorly.

If no indirect hernia is found, then the posterior wall of the inguinal canal must be searched for a direct hernia. Occasionally this may occur through the conjoint tendon itself and will be revealed by further mobilization of the upper flap of the external oblique muscle from underlying structures. An interstitial hernia sac, with the sac lying between the peritoneum and the transversalis fascia, should also be considered, or a herniation of a portion of the bladder. These may be revealed by incising the transversalis fascia. (A recurrent hernia defect through a previous repair may not be obvious if obscured by scar tissue. It may be revealed by careful finger palpation of the previously repaired posterior wall, or by enlarging the deep inguinal ring and inserting a finger to palpate the repair from within, as described for assessing the strength of the posterior wall in a primary indirect repair[3]. A true recurrence must also be differentiated from a previously missed indirect hernia).

It is worthy of note that a hernia sac will normally appear when the intra-abdominal pressure is raised. This is a major advantage of repair under local anaesthesia as the patient can assist by coughing to make the sac appear. In practice, unnecessary dissection can be prevented and time can be saved by pinpointing the sac in this way early in the procedure.

If no hernia sac presents itself, a search must be made outside the inguinal canal. In the more obese patient it may be difficult to differentiate clinically between an inguinal hernia and a femoral hernia. The lower flap of the skin incision should be drawn down and the lower edge of the inguinal ligament defined to the pubic tubercle. Inspection can then be made for a femoral hernia or a prevascular hernia. If the search for a hernia sac should then prove fruitless a reluctant conclusion will have to be made that the swelling was not a hernia in the first place. Other possible swellings include a subcutaneous lipoma, an enlarged lymph gland, a saphena varix or, rarely, a psoas abscess. Inguinal bubos following lymphogranuloma venereum, syphilis or plagues are highly unlikely to be encountered but should be considered in travellers from countries where these conditions occur[4].

After a full search of the posterior wall, even when a hernia has not been found, a repair of the posterior wall of the inguinal canal will probably be necessary to prevent a new direct hernia. Most surgeons now use polypropylene mesh[5]. Finally, a full explanation should be given to the patient after recovery.

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Preoperative radiotherapy for rectal cancer: implications for surgeons, pathologists and radiologists

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Background: Over 10 000 new cases of rectal cancer are reported in the UK each year and adjuvant treatments, such as preoperative radiotherapy, are now being used almost routinely.
Methods: A literature review was performed on the Medline database for English language publications on preoperative radiotherapy and rectal cancer. The radioresponsiveness of rectal cancer, tumour downstaging, radiological staging of irradiated rectal cancer, effects of radiotherapy on anastomotic integrity, anorectal and genitourinary function, the role of preoperative radiotherapy in local excision of rectal cancer, and the histological changes peculiar to radiotherapy were evaluated.
Results and conclusion: Following preoperative radiotherapy, rectal cancer may be downstaged or, occasionally, eradicated histologically. Rectal cancer can now be staged accurately before operation, but this is significantly less reliable following irradiation. The pathological specimen must be examined thoroughly before a tumour can be reported to have been eradicated, especially as unique histological changes are produced by radiotherapy. There is no evidence to suggest that preoperative radiotherapy adversely affects anastomotic integrity. It appears that preoperative radiotherapy has some adverse affects on long-term anorectal dysfunction, but this must not distract from its main objectives in rectal cancer, namely reduced local recurrence rates and improved overall survival.

Paper accepted 7 May 1999

British Journal of Surgery 1999, 86, 1108–1120

Introduction

Over 10 000 new cases of rectal cancer are reported in the UK each year causing 6000 deaths[1]. Following surgery, rectal cancers still recur locally with recurrence rates of 3–32 per cent[2,3]. With the wider introduction of oncologically sound procedures, such as total mesorectal excision (TME), much lower recurrence rates have been reported. Combining surgery and radiotherapy allows macroscopic tumour to be resected, while microscopic disease at the periphery beyond the surgical margins is eradicated by the irradiation.

Local recurrence often reflects a failure of surgery and varies from surgeon to surgeon[4]. Quirke *et al.*[5] reported that 85 per cent of patients, who had involvement of the radial resection margin with carcinoma following surgery for rectal cancer, subsequently developed local recurrence. Heald *et al.*[6,7] have argued that the rectum and mesorectum should be resected *en bloc* (TME) as tumour may be present in the distal mesorectum. It is safe to limit distal mural clearance and thus preserve the anal sphincters, so long as the mesorectum is excised with the cancer[7]. Together with intestinal stapling techniques, better surgery and an improved understanding of limited distal mural and lymphatic spread in rectal cancer[8] have resulted in abdominoperineal resection (APR) making up only 11 per cent of all rectal resections for cancer. Lower recurrence rates are reported with less than 5 per cent local recurrence after 5 and 10 years[9]. A meticulous oncological operation, such as TME, without positive margins may also reduce metastatic disease (developing from local recurrence); MacFarlane *et al.*[9] have reported a 5-year tumour-free survival rate of 78 per cent. Lateral spread does occur but is not adequately dealt with by sphincter-saving surgery or total anorectal resection[8], even if the mesorectum is removed in its entirety. Radical lateral lymphadenectomy has been performed[10], and with some survival benefit, but any perceived long-term advantage is offset by the increased associated surgical morbidity[9] and so extended pelvic lymphadenectomy remains unpopular with most surgeons.

Radiotherapy is aimed at the prevention of local recurrence and there is evidence that overall survival is thereby increased[11,12]. Several approaches are available. Preoperative radiotherapy, which may be either short course for tumours thought to be amenable to surgical resection or long course for those which are fixed clinically or in critical sites, is one approach. Selective postoperative radiotherapy, which should be considered for tumours that involve radial resection margins, is another. Four recent randomized controlled trials of preoperative radiotherapy *versus* surgery alone for rectal cancer have all shown significantly reduced local recurrence rates[11,13–15] and one has demonstrated a survival advantage[11]. However, all of these trials have measured outcome in terms of local recurrence, and disease-free and overall survival. There has been very little discussion about the pathological effects of preoperative radiotherapy to the rectum and pelvis. In this review the following important issues are addressed: the radioresponsiveness of rectal cancer, tumour downstaging, randomized trials of preoperative radiotherapy for rectal cancer, staging of irradiated rectal cancer, the effects of radiotherapy on anorectal and genitourinary function, the role of preoperative radiotherapy in local excision of rectal cancer, and the histological changes peculiar to radiotherapy.

Radioresponsiveness of rectal cancer

The extent of the response to preoperative radiotherapy varies from tumour to tumour, with some being more radioresponsive than others. A marked response (no residual tumour or tumour limited to the rectal wall with no lymph node involvement) to preoperative radiotherapy (45–50 Gy in 25–28 fractions) is seen in 0–57 per cent of rectal cancers[16]. If one was able to identify patients with a radioresponsive tumour at the time of diagnosis, a selective policy of preoperative radiotherapy might be pursued.

It has been shown that anticancer agents may work through apoptosis[17] and not only by their direct harmful effects on actively dividing cells. The *p53* tumour suppressor gene is the most widely mutated gene in human carcinogenesis[18,19] and is involved in apoptosis induced by anticancer agents[20]. Wild-type p53 promotes apoptosis in response to DNA damage[17,21]. Therefore, it is hypothesized that mutations in the apoptosis pathway, including *p53*, could produce tumours that are less radioresponsive or even radioresistant[17]. Furthermore, the *p21* gene is under the transcriptional control of p53 and is necessary for p53-mediated G1 cell cycle arrest. A deficiency of p21 results in compromised radiation-induced cell cycle arrest[22,23]. A recent study investigating the relationship between p53 and p21 expression and radioresponsiveness in human rectal carcinoma[24] found that there was a significant inverse expression of p53 and p21; patients with wild-type p53 were significantly more radioresponsive. Other genes studied include *PCNA* and *Ki-67*[25,26].

These biomarkers may also allow clinicians to identify patients who, despite showing evidence of tumour downstaging following preoperative radiotherapy, remain at risk of tumour recurrence and metastatic spread. Appropriate adjuvant chemotherapy may then be introduced.

Tumour downstaging

Optimal dose of radiotherapy

The tumour node metastasis (TNM) classification is now widely used to describe the depth of invasion of rectal cancers (*Table 1*)[27]. Although local recurrence rates have been shown to be lower with adjuvant radiotherapy, only trials using a dose greater than 20 Gy for preoperative radiotherapy have demonstrated such an advantage over surgery alone[28,29]. Berger *et al.*[29] studied predictive factors of tumour downstaging and showed that a preoperative dose greater than 44 Gy (25 fractions) resulted in a more favourable postoperative staging. Other predictive factors of tumour response were the preoperative clinical stage, tumour differentiation and time before surgery. However, 5-year survival figures confirmed that postoperative staging remained an important prognostic factor. Although it is felt that the dose of preoperative radiotherapy should be 45 Gy[28,30], the optimal fractionation is not known and complication rates increase with the dose per fraction[31].

Table 1 Tumour node metastasis (TNM) staging of rectal cancer[27]

Stage	Description
T_0	No evidence of primary tumour
T_{is}	Carcinoma *in situ* (not used in UK)
T_1	Tumour invades the submucosa
T_2	Tumour invades the mucularis propria
T_3	Tumour invades into the subserosa or perirectal tissues
T_4	Tumour invades other organs and/or breaches the visceral peritoneum
N_0	No lymph nodes involved
N_1	Between one and three lymph nodes involved
N_2	More than three lymph nodes involved
M_x	Metastases unknown
M_1	No metastases
M_2	Histologically confirmed metastases to other organ
R_0	No residual tumour at surgical resection margin
R_1	Microscopic residual tumour
R_2	Macroscopic residual tumour

The addition of concomitant chemotherapy to preoperative radiotherapy improves downstaging[32] and may, therefore, increase the sterilization rate[33]. Other predictors of tumour response include tumour volume and the overall treatment time.

Radiotherapy may improve operability and sphincter-saving procedures

Curative resection may be facilitated through tumour downstaging and, consequently, inoperable rectal cancers may become operable. Together with coloanal anastomosis, this might increase the proportion of sphincter-saving operations being performed[34,35]. Minsky *et al.*[34] described 30 patients with rectal cancer who were judged clinically to require APR. Following preoperative radiotherapy (46·8 Gy), 24 underwent a low anterior resection, with 4-year local recurrence and survival rates of 17 and 75 per cent respectively. Sphincter function was reported to be good in 17 of 22 patients. Rouanet *et al.*[35] reported 21 of 27 patients, who also were judged clinically to require APR, undergoing conservative surgery for distal rectal cancers following preoperative radiotherapy (40 + 20 Gy). None of the tumours in these series was fixed. The presence of apparent downstaging is of importance when selecting patients for postoperative adjuvant chemotherapy. Some patients with a formerly Dukes stage C tumour, who would have received postoperative chemotherapy, may not be offered further treatment if their tumour is downstaged. This is of concern as a survival benefit has been demonstrated in rectal cancer after postoperative radiochemotherapy[36,37]. Clinical decisions are easier if the interval between radiotherapy and surgery is kept below 10 days, as the histological changes are unlikely to be pronounced and downstaging will not yet be apparent.

Regression of primary tumour and lymph nodes

Graf *et al.*[38] looked at the effect of short-term, large-fraction preoperative radiotherapy (25–25·5 Gy given over 5–7 days, with surgery a week later) on possible tumour downstaging. They showed that tumours were significantly smaller and that nodal metastases were less common following radiotherapy. Bozzetti *et al.*[39] studied the effects of preoperative radiotherapy and tumour downstaging with the use of endoscopic ultrasonography carried out before and after radiotherapy prior to surgery. Two of 18 patients showed evidence of downstaging with a significant reduction in tumour diameter. A total dose of 45 Gy was given over 3 weeks, with surgery performed 2–3 weeks later. Histological regression of involved lymph nodes was noted in 13 (28 per cent) of all involved nodes found.

Downstaging following preoperative radiotherapy combined with adjuvant chemotherapy has also been studied[40,41]. In one series all patients with rectal carcinoma were staged before operation with endorectal ultrasonography[40]. Those with T_3 or T_4 lesions were then entered into a protocol of preoperative chemoradiation (45–50·4 Gy for 5–8 weeks), which was followed by further endorectal ultrasonography 1 week before surgery. Ultrasonographic evidence of downstaging as measured by decreased level of invasion and involved nodes was seen in five of 13 patients. Following resection, comparison of pathological staging with the initial endorectal ultrasonography assessment revealed that the level of invasion was downstaged in seven of 15 and the status of involved lymph nodes in seven of nine. Four of 11 patients who had evidence of apparent downstaging had no tumour in the pathology specimen. Chen *et al.*[42] studied the potential downstaging of combined preoperative chemoradiotherapy on advanced rectal carcinomas; 28 of 31 tumours were fixed initially. Patients received a median total radiation dose of 55·8 Gy (25 fractions) with a continuous infusion of 5-fluorouracil (5-FU) throughout the radiation treatment; 23 of 31 tumours showed clinical evidence of downstaging following the combined treatment and six patients had only microscopic residual disease. Twenty-nine patients were able to undergo a complete resection. Before treatment 28 patients had T_4 tumours, whereas following resection 10 patients were staged T_2 and three had T_0 tumours with no residual tumour on pathological assessment (no T_1 tumours).

Complete response rates up to 20 per cent have been reported[43,44], but these series have tended to contain small numbers of patients. Another group studied patients receiving 5-FU, cisplatin and radiotherapy before operation over a 5-week period[41]; 11 of 41 patients had pathological specimens free of tumour microscopically with negative lymph nodes. Nine patients had microscopic disease alone, giving an overall clinical response rate of 49 per cent. A further two patients refused definitive surgery when informed of the clinical response following chemoradiotherapy. Meade *et al.*[45] found that 14 of 20 patients were downstaged following preoperative treatment with 5-FU and high-dose radiation (45–54 Gy in 25 fractions). In seven of 20 patients there was no remaining tumour in the rectal wall or lymph nodes. As the prognosis of rectal cancer is related to the stage of disease at presentation, 5-year survival data for all of these series with impressive results in terms of tumour downstaging are eagerly awaited.

More recently, preoperative hyperthermia has been combined with radiochemotherapy in an attempt to enhance its effects in locally advanced rectal cancer[46]; 37 patients with $T_{3/4}$ rectal cancers were entered into a phase II trial. Twenty-two of the patients had downstaging of the rectal cancer following treatment, and in five patients there was no evidence of residual tumour in the pathological specimen.

It has been hypothesized that the acute side-effects in normal tissue in the field of radiotherapy may be directly proportional to the radioresponsiveness of the tumour[47]. In a prospective randomized trial, patients requiring antidiarrhoeal medication (reflecting bowel toxicity) had significantly smaller tumours at surgery, while patients without significant diarrhoea had more recurrences at follow-up.

Downstaging in randomized controlled trials of preoperative radiotherapy

An overview of all randomized trials of preoperative and postoperative radiotherapy with surgery alone or with each other[48] found that there was a clear dose–response relationship for preoperative radiotherapy in reducing the incidence of local recurrence. This was probably more effective than postoperative radiotherapy. It may be that the malignant cells lateral to the tumour, which cause local recurrence in the pelvis, are a potential source of distant metastases. If this is so, preoperative radiotherapy to well oxygenated, sensitive tissues should improve overall survival rates. The recent Medical Research Council (MRC) trial showed reduced recurrence rates for patients receiving postoperative radiotherapy compared with those in patients having surgery alone[49], although there was no improvement in overall survival. There has been one randomized trial to date of short-course preoperative radiotherapy *versus* postoperative radiotherapy for rectal cancer[50]. This showed a reduced local recurrence rate for patients receiving preoperative radiotherapy, although this was not statistically significant. The new MRC trial (CR07) is designed to address this issue in greater depth.

Quantifying downstaging

Randomized trials of preoperative radiotherapy *versus* surgery alone[11,12,14,51–57] have been examined to ascertain if the phenomenon of tumour downstaging can be quantified (*Table 2*). The two most recent trials of preoperative radiotherapy *versus* surgery alone[12,57] have shown significantly reduced numbers of involved lymph nodes in the surgical specimen following radiotherapy. The Swedish Rectal Cancer Trial[12] protocol involved the delivery of 25 Gy in five fractions to patients with a resectable rectal cancer, resulting in significantly more Dukes A or B tumours in the radiotherapy group ($P = 0{\cdot}008$). The MRC group[57] used 40 Gy over 4 weeks for rectal cancers that were either partially or totally fixed within the pelvis. The number of Dukes C tumours was significantly lower in the radiotherapy group than in the surgery alone group ($P = 0{\cdot}0002$), and it was found that the number of involved lymph nodes was also smaller. Interestingly, a reduced number of Dukes stage C tumours was observed in the first randomized trials of preoperative radiotherapy *versus* surgery alone[51,52]. The authors[51] found these observations difficult to explain and even suggested that a more advanced tumour should be expected in the preoperative radiotherapy group as these patients have a delay to surgery compared with those who have surgery alone.

Two early trials[14,54] reported a group of patients whose tumours underwent complete sterilization following preoperative radiotherapy. In the EORTC trial[14], five (3 per cent) of 166 patients in the preoperative radiotherapy group had no evidence of any tumour in the surgical specimen.

Table 2 Randomized controlled trials of preoperative radiotherapy showing tumour downstaging

Reference	Year	No. of patients	Dose (Gy)	Frequency	Lymph nodes (%)			Sterilization (no. of patients)
					Radiotherapy	Surgery	*P*	
Roswit *et al.*[51]	1975	700	20–25	12 days	24	38	n.a.	n.a.
Toronto[52]	1977	125	5	1 day	37	25	n.a.	n.a.
VASOG II[53]	1986	361	31·5	24 days	35	41	n.a.	n.a.
EORTC[14]	1988	466	34·5	15 days	33	34	n.a.	5
Dahl *et al.*[54]	1990	309	31·5	3·5 weeks	18	28	< 0·05	7
NWRCG[11]	1994	284	20	4 days	No difference		n.s.	n.a.
ICRF[55]	1994	468	15	5 days	43	44	n.s.	n.a.
Stockholm I[56]	1995	849	25	5 days	28	28	n.s.	n.a.
MRC[57]	1996	279	40	4 weeks	30	59	0·0002	n.a.
Swedish[12]	1997	1168	25	5 days	21	29	0·008	n.a.

VASOG, Veterans Administration Surgical Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; NWRCG, Northwest Rectal Cancer Group; ICRF, Imperial Cancer Research Fund; MRC, Medical Research Council; n.a., data not available; n.s., not significant

This group disagree with the argument that radiotherapy is not required in Dukes stage A tumours as three of six deaths in their patients with Dukes stage A disease were attributable to metastatic disease. Although occult metastases may have been present at the time of surgery, it is known that 7 per cent of Dukes stage A tumours may develop local recurrence[58]. The group from western Norway[54] reported that seven (5 per cent) of 155 patients had no residual tumour at histopathological examination following preoperative radiotherapy. They also showed a significantly reduced number of patients having involved lymph nodes following preoperative radiotherapy ($P < 0{\cdot}05$). Three other randomized trials[11,55,56] have found no difference in the number of tumours with involved lymph nodes following preoperative radiotherapy. All of these trials involved short-course radiotherapy (15–25 Gy over 4–5 days).

Adverse effects

It must not be forgotten that preoperative radiotherapy is associated with adverse effects. In two randomized trials, early postoperative morbidity and mortality rates were significantly increased compared with those associated with surgery alone[13,15], particularly cardiovascular and thromboembolic complications. One group examined the late adverse effects of preoperative radiotherapy for rectal cancer in 1027 patients included in two prospective randomized trials[59]. They found that preoperative radiotherapy significantly increased the risk of venous thromboembolism, hip fractures, intestinal obstruction and postoperative fistula. Perhaps more disturbing in an era of increasing use of preoperative radiotherapy for rectal cancer, McCue *et al.*[60] showed in rats that there was an increased risk of colorectal tumour development at the site of anastomosis with irradiation before surgery. This risk was significantly greater in rats receiving a higher dose of irradiation (16 Gy in one fraction *versus* 36 Gy in two fractions). It was suggested that both anastomoses and irradiation alter cell proliferation, resulting in enhanced carcinogenesis.

Preoperative radiotherapy and anastomotic integrity

Low anterior resection is associated with a high incidence of anastomotic complications[61] and, with the increasing use of preoperative radiotherapy, many surgeons are worried about any adverse effect this may have on anastomotic healing[62,63]. Although some authors have reported a high incidence of anastomotic complications following preoperative radiotherapy[50], the only studies specifically addressing such a possible adverse effect have all been performed on rats. Recently, Kuzu *et al.*[64] described an experimental model which mirrored the clinical fractionated preoperative radiotherapy used in clinical trials. Although they were able to show that the anastomotic bursting pressure and hydoxyproline content were significantly reduced in rats that had received preoperative radiotherapy, the clinical outcome was similar to that of the controls. Previous workers have also shown that anastomotic healing is not compromised by preoperative radiotherapy[65], although these authors have been criticized for failure to simulate fractionation as in the clinical setting. Biert *et al.*[66] described a study on rats in which the anastomosis was constructed using normal tissue for the proximal segment and irradiated tissue for the distal segment, as in the clinical setting. They found no differences in anastomotic strength nor hydroxyproline content between the experimental and control groups. In view of the possibility of delayed healing, others have attempted to determine the optimum time to perform an anastomosis following preoperative radiotherapy[67]. It appears, however, that there is no experimental evidence that clinical outcome is adversely affected in patients undergoing anastomosis following preoperative radiotherapy.

Staging of irradiated rectal cancer

In 1974, when radiotherapy was considered to have little place in the treatment of rectal cancer, Papillon[68] reported the use of endocavitary irradiation to cure many early cancers of the lower part of the rectum. Many of the studies of preoperative radiotherapy for rectal cancer described in this review have shown complete eradication of disease in a small subgroup of patients. The presence of tumour in regional lymph nodes can only be detected following removal of the rectum with its mesorectum and, until recently, surgeons have not felt able to leave these rare, completely downstaged, tumours without resection. In a series reported from Brazil[69], 30 patients who were observed to have had a complete response, clinically and radiologically, to preoperative chemoradiotherapy for T_{1-3} rectal cancer were not operated on. Eight have subsequently required surgery for cancer during a follow-up of 3–14 months and two have died from the disease.

Staging after radiotherapy is vital if treatment is to be individualized. If patients could be staged accurately following adjuvant therapy, potentially a local surgical excision, such as by transanal endoscopic microsurgery (TEM), may be employed; surgery might even be avoided altogether. Such staging would also give information about the resectability of locally advanced cancers.

Limitations of imaging after irradiation

Both endorectal ultrasonography and computed tomography (CT) are limited in their ability to give accurate information on the downstaging of rectal cancer following radiotherapy[40,70]. Ultrasonography has a sensitivity of 94 per cent (accuracy 91 per cent) for depth of local invasion of rectal cancer before any treatment modality[71]. This accuracy drops to 47 per cent when measuring depth of invasion following radiotherapy[40]. This difficulty with staging after radiotherapy has been attributed to the radiation-induced changes, such as oedema and fibrosis of the tumour bed and perirectal tissues. The tumour may of course be downstaged, lymph nodes may be sterilized owing to the therapeutic effects of radiotherapy, and water content of the tissues may increase following radiotherapy[70]. Napoleon *et al.*[72] prospectively examined endoanal ultrasonography and pathological staging in 21 patients who had not received, and 19 who had received, preoperative radiotherapy for rectal cancer. Ultrasonography proved accurate in both groups for lymph node involvement, but accuracy for depth of mural invasion was significantly higher in the group who had not had previous radiotherapy (86 *versus* 47 per cent). Most errors in this group consisted of understaging of small T_3 tumours and overstaging of T_2 tumours. After radiotherapy, the rectal wall was found to be thickened and more hypoechoic, and there did not appear to be a clear effect of the interval between finishing radiotherapy and performance of the ultrasound scan.

Another group has compared transrectal ultrasonography and CT staging of rectal cancers before radiotherapy, transrectal ultrasonographic staging following radiotherapy and the pathological stage of the resected specimen for stage T_2/T_3 rectal cancers[70]. Ultrasonography following radiotherapy overstaged the majority of cancers, and correctly determined the depth of invasion and lymph node involvement in only 58 and 68 per cent of patients respectively. However, the positive predictive value for lymph node involvement had increased from 38 per cent before radiotherapy to 50 per cent following radiotherapy. Kahn *et al.*[73] studied the preoperative staging results of 25 patients who were found to have T_0N_0 lesions on pathological examination. They used clinical examination, CT, endorectal ultrasonography and magnetic resonance imaging, and found that most lesions were overstaged following preoperative radiotherapy. However, not all patients underwent all investigations and so the subgroups were small.

As long as staging remains inaccurate, surgeons will continue to perform oncologically appropriate major operations to minimize the risk of leaving radiologically undetected residual tumour. A systematic pathological work-up is essential if one wishes to compare the effects of preoperative radiotherapy between different groups or when deciding on any postoperative adjuvant therapy. Pathological assessment of tumour regression following preoperative chemoradiotherapy has been described previously for carcinoma of the oesophagus[74]. Recently, attempts have been made to define a standard for pathological technique when studying rectal cancer after preoperative radiotherapy[39,75]. Bozzetti *et al.*[39] used the tumour regression grade (TRG) (*Table 3*) proposed by Mandard *et al.*[74] and showed a greater than 50 per cent (TRG 1,2,3) response in 65 per cent of patients undergoing preoperative radiotherapy (45 Gy over 3 weeks) for rectal carcinoma, with one patient having complete regression. More recently, Dworak *et al.*[75] described 17 patients receiving chemoradiotherapy (median 50 Gy) for rectal carcinoma and proposed their own similar grading of regression of tumour. Their grading system showed that 16 patients had had a significant response to the preoperative chemoradiotherapy, but that no patient had complete regression of tumour. It is possible that a pathological staging system for irradiated rectal cancer together with long-term follow-up will reveal which histological features influence survival in these patients.

Table 3 Tumour regression grade for rectal carcinoma treated with chemoradiotherapy[39]

TRG 1	No residual cancer cells
TRG 2	Rare residual tumour cells with marked fibrosis
TRG 3	Marked fibrosis with scattered tumour cells or groups
TRG 4	Abundant cancer cells with little fibrosis
TRG 5	No regression

TRG, tumour regression grade

Effect of preoperative radiotherapy on anorectal and genitourinary function

Anorectal dysfunction is known to occur following low colorectal and coloanal anastomoses. This may be due to a number of factors: direct injury to the internal sphincter[76], disappearance of the rectoanal inhibitory reflex[77] and a reduction in rectal capacity and compliance[78]. Graf *et al.*[79] identified preoperative radiotherapy as one of a number of factors having a negative effect on bowel function after colorectal anastomosis. However, Birnbaum *et al.*[80] performed anal manometry on ten patients before surgery and at long-term follow-up who received preoperative radiotherapy for rectal carcinoma and found no significant differences. A recent randomized trial[81] followed up patients for a minimum of 5 years after short-term, high-dose preoperative radiotherapy for rectal cancer. Median bowel frequency, incontinence of loose stool, urgency and emptying difficulties were significantly greater in the irradiated group. Radiotherapy may affect the bowel wall of the neorectum (although irradiated bowel is likely to be removed), the anal sphincters (the anal canal is irradiated in this group of patients) or the nerve supply of the anorectum.

Genitourinary dysfunction is a serious problem following *en bloc* excision for advanced rectal carcinoma. However, little has been written about the association of preoperative radiotherapy with genitourinary dysfunction. Recently, the postoperative genitourinary function of patients undergoing nerve-sparing surgery alone has been compared with that in those receiving preoperative radiotherapy (42·6 Gy) for advanced rectal carcinoma[82]. No significant difference between the two groups was found in terms of urinary or sexual function. However, significant bladder symptoms (4 per cent; incontinence, frequent haematuria, severe dysuria) and loss of potency (35 per cent) have been reported in patients who have received pelvic radiotherapy (60–66 Gy) for prostatic carcinoma[83]. Such patients experience more anorectal dysfunction but less genitourinary dysfunction than those undergoing radical prostatectomy[84].

Although reduced local recurrence rates must remain the main objective of preoperative radiotherapy, further studies may outline the mechanisms of anorectal dysfunction and allow new techniques to reduce the long-term morbidity. The planning of preoperative radiotherapy now involves a careful definition of tumour volume (a requirement of CR07) and a reduction in unnecessary irradiation of normal tissues.

Role of preoperative radiotherapy in local excision of rectal cancer

At pathological examination 15 per cent of rectal cancers are Dukes stage A[85]. Radical surgery remains the treatment of choice for cancer limited to the bowel wall. However, patients may undergo local resection, and techniques for local excision of rectal tumours (both curative and palliative) include Parks' peranal excision, endoscopic transanal resection and TEM[86].

There are few data on the role of adjuvant radiotherapy in either curative or palliative local excision of rectal tumours, although Papillon[68] has shown that early rectal cancers may be cured by endocavitary irradiation alone. Rouanet *et al.*[87] examined 37 patients undergoing transanal resection for a low rectal carcinoma. Eight received preoperative radiotherapy, 13 received postoperative radiotherapy, and six patients had both preoperative and postoperative treatment (total dose 39·6 Gy); 18 patients had a 'curative' resection for a low superficial tumour, while the remaining 19 were either medically unfit for, or refused, APR. Local recurrence rates were 11 per cent for the 'curative' group and 53 per cent for the unfit group at 5 years. There was a 44 per cent local recurrence rate for large tumours (B1–B2) treated with 40 Gy of preoperative radiotherapy. Survival rates over a similar period were 100 and 35 per cent respectively. Marks *et al.*[88] followed up 14 patients who had received high-dose radiotherapy before a full-thickness resection of rectal carcinoma. The group included 12 patients who were unfit for radical surgery and two whose tumours had been sterilized following radiotherapy; there was a 23 per cent local recurrence rate at 3 years. More recently, another group evaluated postoperative radiotherapy (total dose 45 Gy) in 21 selected patients undergoing local excision of $T_{1-2}N_xM_0$ rectal tumours[89]. Recurrence-free survival at 5 years was 85 per cent, with three patients developing local recurrence.

Minsky *et al.*[90] attempted to predict which patients should receive postoperative radiotherapy following local excision of rectal cancer. They reviewed 168 patients who had undergone curative surgery to determine which clinical and pathological features predict the presence of positive lymph nodes and, therefore, those patients at greatest risk of tumour recurrence after local excision. They recommended surgery alone for patients with stage T_1 tumours and well differentiated adenocarcinomas, as none of these patients were found to have involved lymph nodes. For all other lesions, if there is no evidence of gross tumour in the pelvis, adjuvant radiotherapy to supplement a local excision may prove an alternative to radical surgery. As endorectal ultrasonography provides reasonably accurate staging of rectal cancers, such a policy might be adapted to the use of preoperative radiotherapy and local excision of some tumours. Further trials are required to examine whether it may be used as an adjunct to local excision of favourably staged rectal cancers.

Histological changes following radiotherapy

The histological changes following preoperative radiotherapy for rectal cancer affect both the tumour and normal tissues (*Table 4*). The effect on the tumour may result in several histological changes with tumour regression (*Fig. 1*), while the effect on the pre-existing normal mucosa (*Fig. 2*) may be histological changes that lead to diagnostic confusion.

Tumour

There is at the moment no practical clinical way of assessing which patients' tumours will respond well to radiotherapy and further work is needed on the relevance of pretreatment

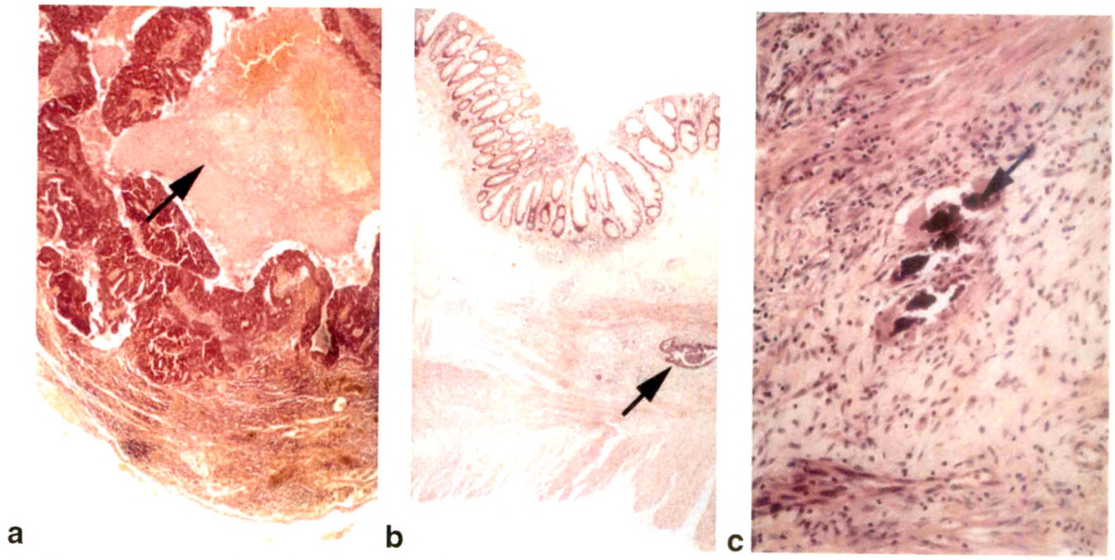

Fig. 1 Effects of preoperative radiotherapy on rectal cancer.
a Eosinophilia necrosis within an adenocarcinoma in a lymph node (arrow); original magnification × 20.
b Small focus of residual carcinoma (arrow) beneath non-tumour mucosa; original magnification × 20.
c Calcification within a foreign body granuloma (arrow) at the site of previous tumour; original magnification × 40

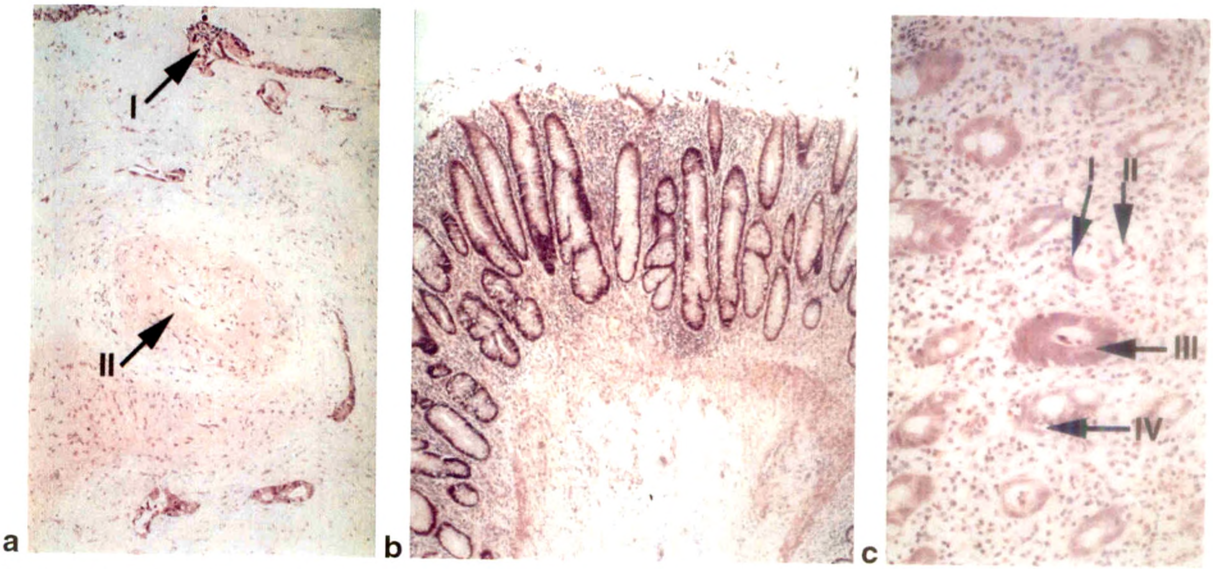

Fig. 2 Effects of preoperative radiotherapy on the adjacent normal rectum.
a Submucosa with residual tumour (I) and irradiation changes in arteriole (II); original magnification × 40.
b Mucosa showing crypt distortion and mild diffuse chronic inflammation, healed over site of previous tumour; original magnification × 40.
c Mucosa showing crypt epithelial withering (I), eosinophil predominant infiltrate (II), severe epithelial regeneration mimicking a unicryptal adenoma of familial adenomatous polyposis (III) and apoptosis in crypt epithelial cells (IV); original magnification × 40

P, 25, 309

Table 4 Histological changes following preoperative radiotherapy for rectal cancer

	Histological features
Tumour	Increased necrosis
	Increased stromal fibrosis
	Foreign body giant cells at site of previous tumour
	Change in shape of advancing tumour edge
	Absence of tumour
	Absence of vascular invasion
	Decreased lymphocytic response
	Colitis cystica profunda
Lymph nodes	Eosinophilic necrosis
	Decreased number
	Decreased size
Normal mucosa	May resemble inflammatory bowel disease, eosinophilic colitis, microscopic colitis, microadenomas of familial adenomatous polyposis, cytomegalovirus colitis

markers[17,24]. The histological changes in the tumour consist of necrosis and stromal fibrosis. It is difficult to establish how much of the necrosis is a radiation effect and how much is due to the tumour outgrowing its own blood supply. Fibrosis around tumours is part of the usual tumour stroma. It may also be induced by inflammation and abscess formation in association with the original tumour. It may be when fibrosis extends deeper than the residual viable tumour and contains foreign body giant cells, granulomas and calcification sometimes in relation to remnants of tumour or pools of mucin, that the tumour had previously reached out as far as the fibrosis.

The shape of the advancing tumour edge is lost as a result of successful radiotherapy and this is important in the Jass staging system for colorectal cancer[91]. The lymphocytic response at the advancing tumour edge is also frequently lost after radiotherapy and therefore cannot be assessed. Absence of vascular invasion after radiotherapy is of unknown significance and this is one of the difficulties in comparing preoperative radiological staging techniques with pathological staging techniques on the resected specimen. Complete absence of tumour in the mucosa is often seen in tumours which respond well to chemoradiotherapy. However, tumour may be present within the deep tissues of the rectal wall and may be present in isolated microscopic foci. If in isolation, these may present diagnostic difficulty in that proctitis cystica profunda (i.e. misplacement of benign epithelium) is a recognized consequence of radiotherapy in the large bowel. So the residual islands of epithelium that may be found have to be scrutinized to ensure that they are genuinely dysplastic and are therefore invasive adenocarcinoma. This feature of complete mucosal absence of tumour also makes it important to resect the rectum and adequately stage the tumour by careful histological examination, taking multiple sections after blocking the entire region of scarring. Sections need to be cut at several levels from these blocks, which should be examined meticulously to identify any small surviving foci of adenocarcinoma. This is essential if the specimen is to be reported as a pathological T_0 tumour.

Lymph nodes

After a long course of radiotherapy lymph nodes may be difficult to find. They will be reduced in number and size and may not contain metastases. Lymph nodes may show tumour with eosinophilic necrosis after a short course of radiotherapy[42]. Some lymph nodes may be outside the field of irradiation, in particular those at the apex of the mesorectum. The presence of tumour in one of these lymph nodes, if it is within 1 mm of the mesorectal plane of excision, conveys a high risk of local recurrence (P. Quirke, personal communication). The mean lymph node harvest after radiotherapy is rarely as high as that from patients without preoperative chemoradiotherapy and careful dissection of the mesorectal fat by the pathologist is required to locate this small number of minute lymph nodes; it may even necessitate processing blindly multiple blocks of mesorectal fat in which no lymph nodes are visible to the naked eye.

Normal mucosa

The changes induced by irradiation in the non-tumour mucosa are many and varied. They depend on the dose of radiation and on the size of the tumour[92]. To the unwary pathologist they give rise to several potential areas of mimicry. The inflammation seen soon after radiotherapy may resemble chronic idiopathic inflammatory bowel disease, eosinophilic colitis and microscopic colitis, until it is realized that there is no crypt architectural distortion, the majority of the inflammatory infiltrate consists of eosinophils and also that the superficial parts of the crypts are withered. Nuclear regenerative changes may give rise to isolated crypts, mimicking the microadenomas of familial adenomatous polyposis. The regenerative nuclear changes may also include large eosinophilic nucleoli which, in the background of inflammation, may simulate cytomegalovirus colitis. Later in the course of the radiation changes there may indeed be crypt architectural distortion and fibrosis of the lamina propria with only scattered eosinophils, which makes for a difficult distinction between a postirradiation picture and quiescent inflammatory bowel disease. However, if the submucosa is available for examination, considerable fibrosis is noted along with intimal thickening of submucosal blood vessels[92].

Summary

The histological changes in the pre-existing normal mucosa need to be appreciated by the histopathologist to avoid erroneous concurrent diagnosis. Staging after radiotherapy needs to be stated clearly in the pathology report as *postradiotherapy* pathological TNM stage. It may be that prechemoradiotherapy staging has a greater effect on prognosis and only careful long-term follow-up studies will determine this. T_0 tumours vary in proportion from study to study and each study may well have had the specimens dissected in a slightly different way. It is the authors' opinion that the entire scarred area should be examined histologically before issuing a T_0 report.

Conclusion

Recent randomized control trials of preoperative radiotherapy for rectal cancer have demonstrated reduced local recurrence rates and improved survival. Following preoperative radiotherapy, the rectal cancer may be downstaged or even completely eradicated histologically, but not necessarily biologically. Rectal cancer can now be staged adequately before operation, but accuracy falls significantly following irradiation. This may affect whether a patient has sphincter-saving surgery and further adjuvant therapy. The pathological specimen must be examined thoroughly before a tumour can be declared to have been eradicated, and there are histological changes following treatment that are unique to radiotherapy. There is no evidence to suggest that preoperative radiotherapy adversely affects anastomotic integrity. Preoperative radiotherapy has some adverse affects on long-term anorectal dysfunction, but this must not distract from its main objectives, namely reduced local recurrence rates and improved overall survival.

Acknowledgements

J.M.D.W. has been awarded the Ivo Fuchs Colorectal Cancer Research Fellowship funded by the Waverley Trust.

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ANNOUNCEMENT

Further improvements in the editorial process

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Management of liver trauma

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Background and methods: Management of blunt or penetrating injuries to the liver remains a significant challenge. This review discusses the mechanisms of liver injury, grading system for severity, available diagnostic modalities and current management options. It is based on a Medline literature search and the authors' clinical experience.

Results: Unstable patients require immediate laparotomy, but selected patients who are haemodynamically stable may be managed without operation. The preferred operative techniques include resectional debridement, hepatotomy with direct suture ligation and perihepatic packing; anatomical resection, hepatic artery ligation and various bypass techniques have a limited, more defined role for selected injuries. Major complications include haemorrhage, sepsis and bile leak.

Conclusion: Enhanced resuscitation, anaesthesia and intensive care have contributed to a significant reduction in mortality rates from liver trauma. Optimum results are obtained with a specialist team that includes an experienced liver surgeon, anaesthetist, endoscopist and interventional hepatobiliary radiologist with expertise in managing postoperative complications.

Paper accepted 12 May 1999

British Journal of Surgery 1999, 86, 1121–1135

Introduction

Despite its relatively protected location, the liver is the most frequently injured intra-abdominal organ[1], although splenic injuries are more common following blunt abdominal trauma[2]. Associated injuries to other organs, uncontrolled haemorrhage from the liver and subsequent development of septic complications contribute significantly to morbidity and death[3]. Although mortality rates from liver trauma have reduced over the past few decades, the surgical management of liver injuries remains a challenging problem for the general surgeon. This article reviews the mechanisms of liver injury, grading system for severity, available diagnostic techniques and current management options.

Mechanisms of injury

Violent behaviour and road traffic accidents account for the majority of liver injuries. Liver injuries secondary to blunt trauma are typical in Europe (80–90 per cent of all liver injuries)[4–6], while penetrating injuries account for 66 per cent of liver trauma in South Africa[7] and up to 88 per cent in North America[8–10].

Two types of blunt liver trauma have been described. Deceleration injuries occur in road traffic accidents and in falls from a height when, on impact, the liver continues to move, thereby producing a laceration of its relatively thin capsule and parenchyma at the sites of attachment to the diaphragm. The liver usually tears between the posterior sector (segments VI and VII) and the anterior sector (segments V and VIII) of the right lobe (*Fig. 1*). In contrast, a direct blow to the abdomen, by a fist or any blunt object, may lead to a crush injury, with damage to the central portion of the liver (segments IV, V and VIII). Compression between the lower right ribs and the spine may also cause bleeding from the caudate lobe (segment I)[11]. Blunt trauma may cause disruption of the hepatic substance beneath an intact Glisson capsule, resulting in a subcapsular or intraparenchymal haematoma.

Penetrating injuries are usually associated with gunshot or stab wounds, with the former usually resulting in more tissue damage due to the cavitation effect as the bullet traverses the liver substance.

Grading system for liver injuries

The severity of liver trauma ranges from a minor capsular tear, with or without parenchymal injury, to extensive disruption involving both lobes of the liver with associated hepatic vein or vena caval injury. In 1989, the Organ Injury Scaling Committee of the American Association for the Surgery of Trauma produced a Hepatic Injury Scale[12] which was revised in 1994[13] and is currently regarded as the standard by which hepatic injuries are described in most major trauma centres (*Table 1*). Grade I or II injuries are considered minor; they represent 80–90 per cent of all cases and usually require minimal or no operative treatment[1,14]. Grade III–V injuries are generally considered severe and often require surgical intervention, while grade VI lesions are regarded as incompatible with survival.

Patient assessment and initial investigation

The initial assessment and management of an injured patient should proceed according to the Advanced Trauma Life Support guidelines of the American College of Surgeons Committee on Trauma[15]. A conscious patient, who is haemodynamically unstable following blunt trauma and has generalized peritonism, should undergo immediate laparotomy without further investigation. If the patient is neurologically impaired or physical signs are equivocal, a diagnostic peritoneal lavage (DPL) should be undertaken and an immediate laparotomy performed if the test is positive[16–18]. However, if the patient is haemodynamically stable, further radiological assessment should be undertaken.

A gunshot wound to the abdomen is an indication for laparotomy regardless of the physical signs, as it is difficult to assess the damage caused by a bullet without surgical exploration[10]. Urgent laparotomy is also indicated in patients who have sustained a stab wound to the abdomen and are haemodynamically unstable. If the patient is stable and a liver injury is suspected, imaging studies should be performed.

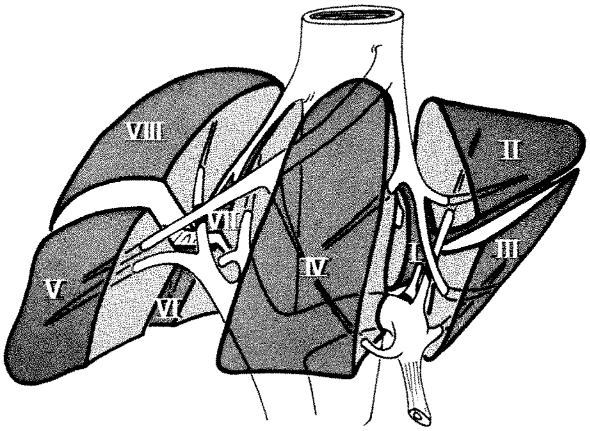

Fig. 1 Segmental division of the liver according to Couinaud's nomenclature

Ultrasonography

Abdominal ultrasonography is often used as the initial radiological technique to assess for hepatic injury. Early and rapid assessment can be obtained in the casualty department and many major trauma centres in the USA, Europe and Japan are now using abdominal ultrasonography and computed tomography (CT) in preference to DPL[19–22]. Several recent prospective studies have reported that abdominal ultrasonography can be performed with a sensitivity of 82–88 per cent and a specificity of 99 per cent in detecting intra-abdominal injuries[23–25], but it remains operator dependent.

Table 1 Grading of liver injuries[13]

Grade*	Injury	
I	Haematoma	Subcapsular, less than 10 per cent surface area
	Laceration	Capsular tear, less than 1 cm parenchymal depth
II	Haematoma	Subcapsular, 10–50 per cent surface area Intraparenchymal, less than 10 cm in diameter
	Laceration	1–3 cm parenchymal depth, less than 10 cm in length
III	Haematoma	Subcapsular, more than 50 per cent surface area or expanding Ruptured subcapsular or parenchymal haematoma Intraparenchymal haematoma more than 10 cm or expanding
	Laceration	More than 3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25–75 per cent of hepatic lobe or one to three Couinaud segments within a single lobe
V	Laceration	Parenchymal disruption involving more than 75 per cent of hepatic lobe or more than three Couinaud segments within a single lobe
	Vascular	Juxtahepatic venous injuries, i.e. retrohepatic cava/central major hepatic veins
VI	Vascular	Hepatic avulsion

*Advance one grade for multiple injuries, up to grade III

Computed tomography

Detection of solid intra-abdominal organ injuries in stable patients by CT has become the standard evaluation method despite the fact that grading of blunt hepatic injuries by CT does not correlate precisely with subsequent operative findings[26]. CT has high sensitivity and specificity for detecting liver injuries which increase as the time between injury and scanning increases, evidently because haematomas and lacerations become better defined[27](*Fig. 2*).

Although CT is very useful in the evaluation of stable patients with abdominal trauma, most authors agree that unstable patients, with either blunt or penetrating trauma, are unlikely to benefit from this investigation because of the valuable time that it requires[17]. Dilute (2–5 per cent) water-soluble oral contrast agent (500–750 ml) is administered via mouth or nasogastric tube 20–40 min before the investigation; 100–200 ml of intravenous contrast agent is then administered 70–90 s before initiation of the scan. Biphasic helical CT is performed with scanning in the arterial enhancement phase and later organ enhancement phase using sections 5–8 mm thick. Evidence of extraluminal contrast agent may indicate coexistent bowel injury[28].

Laparoscopy

Diagnostic laparoscopy has been used successfully in penetrating trauma[29–31], but its role in blunt abdominal trauma is not well defined[32]. The benefits of laparoscopic assessment include reducing negative and non-therapeutic laparotomy rates, patient morbidity rates, hospital stay and treatment costs[30,31,33]. Limited therapeutic intervention may also be possible in a small number of patients[34].

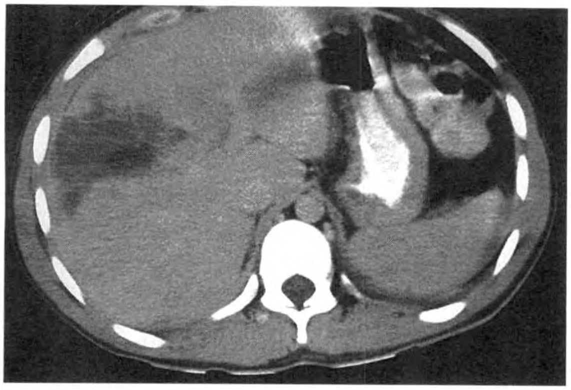

Fig. 2 Computed tomography scan demonstrating a deep laceration of the right lobe of liver secondary to blunt abdominal trauma

Non-operative management of liver injuries

The recognition that 50–80 per cent of liver injuries stop bleeding spontaneously[21,35,36] and the increasing trend towards conservative management of splenic trauma have led to a non-operative approach for blunt liver trauma in haemodynamically stable patients. Furthermore, CT has contributed to a generalized acceptance of this method as an effective therapeutic strategy for liver injuries[37].

Initial reports of non-surgical management dealt with minor liver injuries[14,18,38–42], but recently more serious injuries (grade III–V) have been successfully managed without surgery[6,36,43–45]. To date, there have been more than 1000 reported cases of blunt liver trauma treated without operation[21]. A review of 495 patients from the recent literature noted a success rate with this form of treatment of 94 per cent[37]. This was accomplished with a mean transfusion rate of 1·9 units, a complication rate of 6 per cent (of which only 3 per cent was haemorrhage related) and a mean hospital stay of 13 days. There were no liver-related deaths, nor were there any missed enteric injuries. Similar results were described in a multicentre report of 404 blunt hepatic injuries[46]. It should be noted that the quoted success rates may not represent the overall results of non-operative management of liver injuries, as poorer results may not be offered to scientific journals.

Selection criteria for non-operative management

Since the initial report on conservative management of blunt liver injuries in four paediatric patients in 1972[47], various criteria have been used in the selection of patients for this form of treatment. In 1985, Meyer *et al.*[48] recommended the following clinical criteria: haemodynamic stability, absence of peritoneal signs, good quality CT scans, an experienced radiologist, the ability to monitor patients in an intensive care setting, the facility for immediate surgery if required, a simple parenchymal laceration or intrahepatic haematoma with less than 125 ml of free intraperitoneal blood and no other significant intra-abdominal injuries. Farnell *et al.*[49] subsequently extended the threshold of haemoperitoneum to 250 ml and introduced specific CT requirements. These included subcapsular or intraparenchymal haematomas, unilobar fracture, absence of devitalized tissue and absence of other intra-abdominal injuries. Recently, Feliciano[50] suggested that any blunt hepatic injury, regardless of its magnitude, should be managed without operation if the patient is haemodynamically stable and has a haemoperitoneum of less than 500 ml. Most authors currently believe that the ultimate decisive factor in favour of non-operative management should be the haemodynamic stability of the patient at presentation or after initial resuscitation, irrespective of the grade of injury on CT or the amount of haemoperitoneum[18,22,37,43,45,50,51].

Potential complications of non-operative management

There remain many areas of concern when a non-operative policy is chosen, namely the discrepancy between CT and operative findings for blunt liver injuries[26], the risk of missing other intra-abdominal injuries with sole reliance on CT images, the potential for transmission of bloodborne viral illnesses from repeated blood transfusion, and the risk of continued haemorrhage, haemobilia, bile leak and sepsis. However, a recent study has shown that the risk of missing other intra-abdominal injuries can be reduced with the use of DPL to increase the diagnostic yield of CT in cases with equivocal clinical findings, and that patients treated without operation required significantly fewer blood transfusions than a surgically treated group with comparable liver injuries[45]. Furthermore, complication rates in patients undergoing non-operative treatment have been shown to be no greater than those in patients treated surgically[52].

Monitoring of patients using a non-operative policy

Documentation of either improvement or resolution of the hepatic injury by CT was once considered an essential criterion for continuing with a non-operative approach[43], but this no longer seems to be necessary and no alteration in management is indicated unless there is some change in the patient's clinical course[45]. In an analysis of 404 patients, 206 (51 per cent) did not undergo follow-up CT and none experienced untoward effects as a result of not having a 'second' scan[46]. Therefore, repeat abdominal CT scans should be obtained only if indicated clinically.

Failure of non-operative management

Failure of non-operative management occurs in almost all series. However, it appears that the natural course of liver injuries is more analogous to that of lung or kidney injuries, rather than splenic injuries, in that any deterioration is usually gradual, with a fall in haemoglobin level or an increase in fluid requirement, rather than acute haemodynamic decompensation[45]. Therefore, with close supervision, patients who fail with an initial non-operative approach can be detected early and treated appropriately.

Summary

Non-operative management of blunt liver trauma has been shown to be safe in selected patients, thereby reducing the number of unnecessary laparotomies. Of all the variables evaluated, haemodynamic stability appears to be the most crucial and has become the decisive factor in favour of undertaking non-operative management.

Operative management of liver injuries

Despite the current trend towards conservative treatment, a significant number of patients will require urgent surgical intervention. If possible, the patient should be resuscitated in the emergency room, although it is important not to prolong preoperative resuscitation, since vital time can be lost without achieving haemodynamic stability[10]. Vital prerequisites for a successful outcome are an experienced surgeon who is familiar with the surgical anatomy of the liver, adequate blood, platelets, fresh frozen plasma and cryoprecipitate, a fully equipped intensive care unit and the necessary diagnostic back-up to monitor and detect potential complications. In the absence of any of these requirements, the patient should be transferred to the nearest available specialized unit for definitive treatment after initial control of haemorrhage[11,14].

Operation and initial control of bleeding

At operation, skin preparation should allow for extension of a midline abdominal incision to a median sternotomy or right thoracotomy, if necessary, for adequate exposure of posterior liver injuries[10,53]. If the indication for surgery is an obvious penetrating through-and-through liver injury, a bilateral subcostal incision is a useful alternative. If a major liver injury is encountered, initial control of bleeding can be achieved with temporary tamponade of the right upper quadrant using packs, portal triad occlusion (Pringle manoeuvre), bimanual compression of the liver or even manual compression of the abdominal aorta above the coeliac trunk[54,55]. At this point, further evaluation of the extent of the injury should be delayed until the anaesthetist has adequately replenished the intravascular volume and stabilized the blood pressure[14]. Attempts to evaluate the liver injury before adequate resuscitation may result in further blood loss and worsening hypotension.

Digital compression of the portal triad (Pringle manoeuvre) can be used diagnostically and compression can be maintained with an atraumatic vascular clamp if haemorrhage decreases[56]. The clamp should be occluded only to the degree necessary to compress the blood vessels in order not to injure the common bile duct. If haemorrhage is unaffected by portal triad occlusion, major vena cava injury or atypical vascular anatomy should be suspected[57,58]. Although the permitted occlusion time of the portal triad is controversial, most authors now agree that clamping of the hepatic pedicle for up to 1 h is well tolerated with no adverse effects on liver function[10,28].

After initial intraoperative resuscitation, the liver must be mobilized adequately to allow a thorough examination of the damaged area, unless the injury is already accessible through the incision[10,55,59]. The liver is mobilized by dividing the falciform, triangular and coronary ligaments, and by placing abdominal packs posteriorly to maintain this position[14]. This manoeuvre allows the surgeon to determine the nature and severity of the injury and to decide on the necessary surgical technique. Care should be taken to avoid impairing venous return, by either excessive lifting and/or rotation of the mobilized liver, or excessive packing causing caval compression[14].

Hepatorrhaphy

This was one of the earliest techniques described, initially introduced in 1897[60]. Large horizontal mattress sutures can be used to compress liver parenchyma and bleeding vessels. However, several serious complications have been reported using this technique, including extensive tissue necrosis due to compression required to arrest haemorrhage also rendering the included liver parenchyma avascular. This may predispose to sepsis[1,14,61–63]. Although hepatorrhaphy has fallen out of favour in the past decade, many believe that it is useful in minor liver injuries (grade I and II)[41,42], or when dealing with critically ill patients in whom more extensive techniques would be inappropriately time consuming[1].

Hepatotomy with direct suture ligation

This is a commonly used technique for severe parenchymal liver injuries. It involves division of normal hepatic parenchyma, i.e. extending liver lacerations using the finger fracture technique[21], electrocautery[14] or an ultrasonic dissector, in order to expose damaged vessels and hepatic ducts which can then be ligated, clipped or repaired under direct vision. A low incidence of rebleeding, necrosis and sepsis has been reported with the use of this technique. Pachter *et al.*[42] recorded a morbidity rate of 8 per cent and a mortality rate of 5 per cent in a large number of patients with grade III and IV parenchymal injuries, and Beal[3] reported an 87 per cent success rate. Most of the large series describing this technique report penetrating liver injuries[8,64–66] and so its effectiveness following blunt liver trauma requires further evaluation[67].

Resectional debridement

This involves removal of all devitalized tissue down to normal hepatic parenchyma using the lines of injury, rather than anatomical planes, as the boundaries of resection. The portal triad is usually clamped first and the finger fracture technique or an ultrasonic dissector is used to dissect just outside the area of injury. Small hepatic ducts and blood vessels can be easily identified and ligated[54]. It is rapid compared with standard anatomical resections, which are more time consuming and remove more normal liver parenchyma. Resectional debridement of all devitalized parenchyma reduces the risk of postoperative sepsis, secondary haemorrhage and bile leakage[14]. Rarely, a major segmental bile duct will be disrupted without disruption of the associated blood supply to that segment. If this is identified, the involved liver parenchyma should be resected, even if it is vascularized and appears viable, in order to reduce the risk of a subsequent biliary fistula.

Anatomical resection

Anatomical resection for major liver trauma was introduced in the 1960s, but soon fell out of favour owing to the associated high mortality rate. By definition, this is performed along anatomical planes and usually requires initial identification of portal structures[68,69]; some authors propose rapid hepatectomy with no hilar ligation, as introduced in the Vietnam war[21,28]. Anatomical resections are currently performed in approximately 2–4 per cent of patients with liver trauma[9,57,58], with a mortality rate approaching 50 per cent in most series[3,54,70]. The magnitude of liver injury, coexistent shock, coagulopathy, acidosis, and associated injuries to other organs are responsible for this high mortality rate[67]. It is generally accepted that anatomical resections should be reserved for situations in which no other procedure adequately achieves haemostasis. Deep lacerations involving major vessels or bile ducts, extensive devascularization and major hepatic venous bleeding are indications for this type of surgical management provided that all other less aggressive techniques have failed[3,10,28,58,67,71].

Selective hepatic artery ligation

Although this technique was previously very popular for controlling arterial bleeding from hepatic injuries, it is now rarely used as other techniques are usually sufficient to arrest haemorrhage[10,14,28,72,73]. When arterial bleeding does not stop with selective hepatic artery ligation, the presence of accessory hepatic arteries originating from the superior mesenteric or left gastric artery should be suspected[63]. If the right hepatic artery is ligated, the gallbladder should be removed to avoid necrosis of that organ[74]. Opponents of selective hepatic artery ligation argue that arterial ligation increases the risk of postoperative hepatic insufficiency[11,75,76]; however, the incidence of ischaemia following this technique is reported to be very low because of the oxygen delivery capacity of the portal blood[54,73]. Selective hepatic artery ligation can be justified when the source of bleeding cannot be identified in a hepatotomy site, or if perihepatic packing fails to control haemorrhage and temporary hepatic artery occlusion at the portal triad appears to be effective[3,11,14,63]. Contraindications to hepatic artery ligation include bleeding from portal or posthepatic veins and cirrhosis[54,73].

Perihepatic packing

Packing of liver injuries was discouraged after the experience of serious complications in World War II and the Vietnam war. However, during the past decade, perihepatic packing has been re-established as an acceptable method of managing liver injuries in certain situations[7,8,77–82] and is currently undertaken in 4–25 per cent of patients requiring operative management of hepatic injuries[54,79].

Packing should be considered seriously when other surgical methods of arresting haemorrhage fail in a haemodynamically unstable patient. Uncontrollable coagulopathy is an absolute indication for perihepatic packing[83]; others include bilobar liver injury, large non-expanding haematoma and capsular avulsion[14]. Recently, packing has been used successfully when dealing with suspected injury to the vena cava or hepatic veins[3,14,84]. It is also a useful adjunct to the inexperienced surgeon's armamentarium for patients who need to be temporarily stabilized for transfer to a specialist centre[11,14].

The appropriate timing for packing remains controversial, although many authors believe that it should be employed when coagulopathy is suspected and long before irreversible shock from blood loss, hypothermia and acidosis ensues. Packing therefore should be applied when blood loss transfusion requirements exceed 10 units, core body temperature falls below 32°C, pH falls below 7·2, or if there are clinical signs of a diffuse coagulopathy[83,84].

Intrahepatic packing, in which packs are forced into deep fractures, should not be used as this manoeuvre can extend the injury further and increase bleeding. The technique of perihepatic packing involves manual closure or approximation of the parenchyma, followed by the sequential placing of dry abdominal packs or a single rolled gauze around the liver and directly over the injury in an attempt to provide tamponade to a bleeding wound (*Fig. 3*). The minimal number of dry laparotomy pads necessary to arrest haemorrhage should be used so that vena caval compression is avoided[85]. The recent introduction of plastic sheets between the packs and liver tissue minimizes the risk of recurrent bleeding on pack removal[79]. Subhepatic packing may be used to compress the liver parenchyma against the diaphragm, but there is a significant risk of infrahepatic caval and renal vein compression with this technique.

Rapid abdominal closure following perihepatic packing is recommended for all critically ill patients before immediate transfer to the intensive therapy unit. Most surgeons employ skin closure only, leaving the fascia for primary closure at the subsequent procedure for pack removal[27,86]. The presence of packs, combined with massive oedema of the bowel, may lead to difficulties in wound closure. If this is encountered, a mesh can be inserted to prevent further compromise of ventilation and bowel viability, and to avoid pressure necrosis of the liver[82].

Perihepatic packs should be removed as soon as the patient is stable and coagulopathy, hypothermia and acidosis have been corrected[42,79]. This usually takes 12–36 h. Broad-spectrum antibiotics should be administered when packs are *in situ* to minimize the risk of sepsis[63,87] which has been reported to occur in 10–30 per cent of patients[9,28,78,79,82].

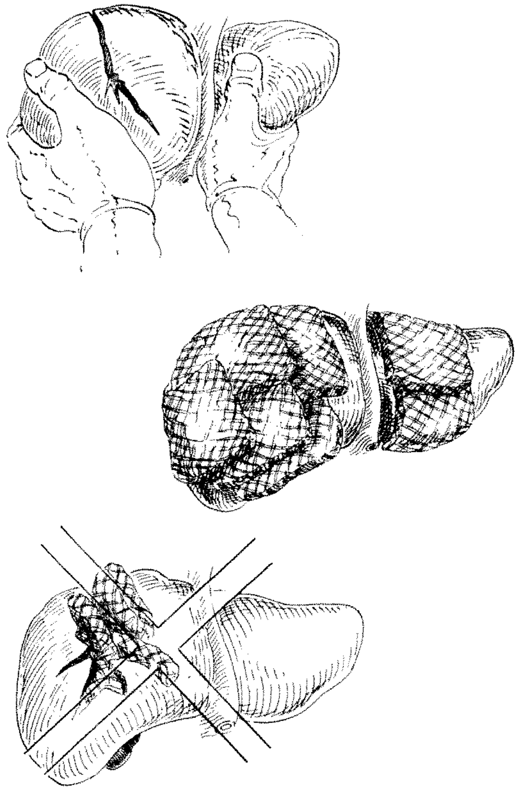

Fig. 3 Procedure for packing of liver injuries demonstrating manual compression of the liver parenchyma to close the hepatic defect with sequential placing of packs. Do not force packs into the fracture

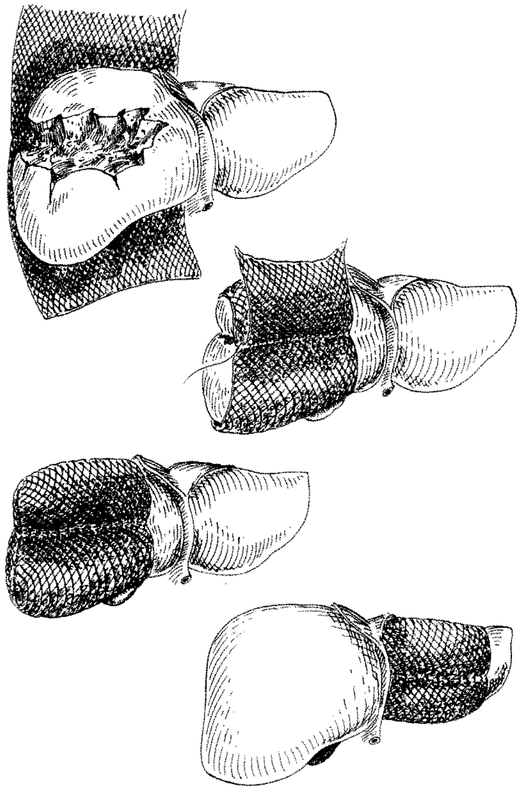

Fig. 4 Mesh wrapping is performed by placing a piece of absorbable mesh around the injured lobe of liver and suturing the mesh under tension to provide a tamponading effect

Mesh wrapping

The use of this relatively new technique has been particularly advocated for major parenchymal disruptions, i.e. grade III–IV lacerations, or for tamponading large intrahepatic haematomas, thus minimizing the risk of a delayed rupture[14,17,28,88–90]. It is not indicated where juxtacaval or hepatic vein injury is suspected. Unlike intra-abdominal packing, a relaparotomy is not routinely required and mesh wrapping does not seem to compromise respiratory or renal function as it does not increase intra-abdominal volume or pressure, and so abdominal closure is much easier[17,89]. Furthermore, it does not require the experience needed to perform an anatomical resection[89]. However, there is some concern about the amount of time needed to apply the mesh wrap in a haemodynamically unstable patient who might be best treated with rapid insertion of perihepatic packs[28].

Several mesh wrapping techniques have been described[17,88,89]. Two sheets of a synthetic absorbable mesh are sutured together, either on two adjacent sides to create a 'pitta pocket', or longitudinally to wrap the liver in a 'cigarette roll', and secured anteriorly and posteriorly (*Fig. 4*). A cholecystectomy should be performed whenever the wrap is applied to the right lobe of the liver to avoid necrosis of the gallbladder wall. Experimental studies on animals suggest that mesh wrapping can effectively control bleeding and improve survival[88,91]. To date, only limited clinical experience has been reported and, although initial results are encouraging, with an overall mortality rate of approximately 20 per cent[17], further evaluation of this technique is necessary.

Omental packing

The use of omentum for haemostatic purposes in managing major hepatic injuries was first described by Stone and Lamb in 1975[92]; it is used infrequently today. After initial control of any major bleeding, a viable omental pedicle can be placed in the depth of the hepatic wound to stop oozing from the low-pressure venous system of the liver parenchyma and also to fill any dead space that may later predispose to formation of an abscess[21,42]. The omental pack is held in place with absorbable sutures that cross the wound edges. Potential advantages of the use of viable omentum are that it is autogenous tissue and so does not require reoperation for removal, and there is evidence to suggest it minimizes the risk of postoperative sepsis[14,28,54,93,94].

Intrahepatic tamponade with Penrose drains

Low-velocity gunshot wounds and stab injuries to the abdomen may result in well defined tracts through the liver substance. In some cases, the tract may be so long that hepatotomy and direct suture ligation would be very extensive. Several techniques have been proposed to control tract bleeding in such situations without the need for hepatotomy. Several Penrose drains can be passed through the defect under tension[14,95]. When the tension is released, the drains shorten and tamponade the walls of the wound. The drains can then be brought out through the midline incision.

Alternatively, bleeding can be controlled by balloon tamponade[96,97] (*Fig. 5*). A Penrose drain is passed over a red rubber catheter, and the proximal and distal ends of the drain are ligated securely around the catheter. The device is then passed through the tract and the drain is inflated with saline and contrast agent, tamponading any bleeding vessels and allowing radiographic investigation in the postoperative period if necessary. The proximal end of the catheter is brought through the abdominal wall to the skin. In a recent collective review, 35 patients with penetrating wounds to the

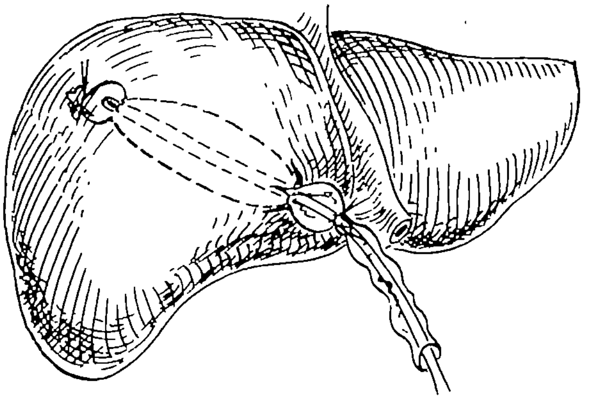

Fig. 5 Balloon tamponade of a through-and-through wound of the liver

liver were treated successfully with balloon tamponade[97] but, in general, this technique has limited application.

Adjunctive techniques

Fibrin glue, a combination of fibrinogen, thrombin and calcium chloride, has been found to be very effective in controlling oozing from raw liver surfaces. It also accelerates wound healing, inhibits growth of bacteria and may reduce the risk of developing postoperative haemorrhage or bile leakage by sealing small blood vessels and bile ducts[14,40,98–100]. Disadvantages of fibrin glue include hypotension if the agent enters the bloodstream, which has led to the death of two patients[101], and the theoretical risk of viral transmission (hepatitis or human immunodeficiency virus)[98,99].

Retrohepatic venous injuries

Retrohepatic venous injuries are the most challenging of all cases of liver trauma, occurring in approximately 8–15 per cent of hepatic injuries, most commonly following blunt abdominal trauma[102,103]. Injury of the retrohepatic vena cava or the hepatic veins should be suspected immediately if portal triad occlusion fails to control bleeding or if the injury extends to the bare area of the liver on palpation. There is still great controversy as to the best operative approach to these injuries. Several surgical techniques have been advocated with the optimal approach yet to be determined. While minor retrohepatic venous injuries may be repaired by direct suture, major injuries require more demanding measures, such as total vascular exclusion, insertion of an atriocaval shunt or venovenous bypass to control bleeding before surgical repair.

Total vascular exclusion

Total vascular exclusion was initially described by Heaney *et al.*[104] for elective liver resections and was subsequently applied in major retrohepatic venous injuries with uncontrollable haemorrhage[102]. It involves clamping of the portal triad (Pringle manoeuvre) and the infrahepatic and suprahepatic vena cava[53,104,105] (*Fig. 6*). Although some investigators advocate that it can be performed more rapidly and with less blood loss than atriocaval shunting or venovenous bypass[11,102,106], it has fallen out of favour. Clamping of the inferior vena cava results in a sudden decrease of venous return and profound hypotension, requiring major transfusion to maintain adequate cardiac output in an already hypovolaemic patient. Moreover, significant cardiac arrhythmias may result with the abrupt wash-out of cardiotoxic gut metabolites on release of the clamps[14,71,89].

Venovenous bypass

Venovenous bypass offers several advantages in the trauma setting in that it maintains good venous return to the heart, it does not require heparinization, and it potentially allows decompression of the portal system, thereby minimizing bowel oedema and avoiding reperfusion of toxic gut-derived products of ischaemia[11,105,107–110]. The technique involves insertion of a shunt from the left common femoral vein to carry blood through a centrifugal vortex pump with outflow to either the left axillary vein or left internal jugular vein. Control of the portal vein and hepatic artery is established using the Pringle manoeuvre, and the vena cava is clamped suprahepatically and infrahepatically above the level of the renal veins. The portal system is drained by inserting a cannula into the inferior mesenteric vein. Since there is limited experience with its use in the trauma setting, the adequacy of this technique has yet to be determined.

Atriocaval shunting

Atriocaval shunting was introduced by Schrock *et al.* in 1968[111]. A large-bore chest tube is inserted into the right atrial appendage, advanced into the inferior vena cava to a level just proximal to the renal veins, and secured in position using tapes above and below the liver. Insertion of the shunt along with clamping of the portal triad allows total vascular isolation of the liver, thereby decreasing blood flow through the injured area while preserving venous return to the right atrium. Unfortunately, the use of atriocaval shunting for retrohepatic venous injuries is associated with a mortality rate of 50–90 per cent in most major trauma centres[3,9,112–118]. Feliciano, Pachter and co-workers[54,113]

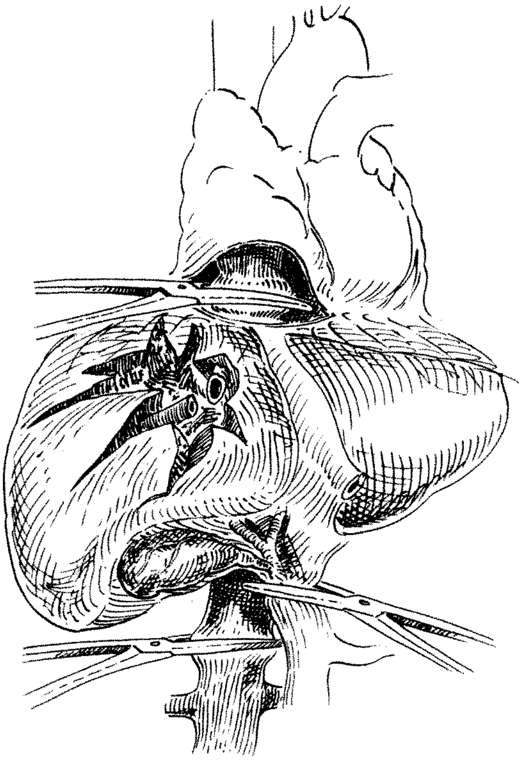

Fig. 6 Total vascular exclusion of the liver with vena cava and porta hepatis control

have emphasized that delay in diagnosis of a retrohepatic injury resulting in coagulopathy and hypothermia, and inexperience in shunt placement, are the most important factors directly related to this increased mortality rate. In an attempt to avoid thoracotomy, purpose-built balloon shunts inserted via the saphenofemoral junction have been introduced recently[119]. The retrohepatic veins are tamponaded by the balloon while blood flow is maintained through the tube.

Non-shunting approach to retrohepatic venous injuries

Pachter *et al.*[42] used a rapid direct approach to retrohepatic venous injuries, with prolonged portal triad occlusion and a finger fracture technique through normal parenchyma, in nine patients, of whom six survived. Similar survival rates using this non-shunting approach have been reported by others[115,117,120].

Although packing is generally considered a useful surgical approach only for parenchymal liver injuries, Beal[3] has recently introduced perihepatic packing as an effective treatment for retrohepatic venous injuries; no patient died from exsanguination. Based on these findings, several authors have suggested initial packing of retrohepatic venous injuries and, if bleeding stops, conclusion of the operation; if packing is ineffective a vascular exclusion technique should be performed and repair attempted[3,14,28,71,85].

Liver transplantation

Liver transplantation has recently been used as a last resort in a small number of patients with irreparable liver injuries[121–124]. Ringe *et al.*[124] introduced a two-stage approach, involving total hepatectomy with construction of an end-to-side portacaval shunt to allow adequate bowel perfusion, followed by liver transplantation when a donor liver is available. Liver transplantation in the trauma setting may be life-saving when all other measures fail to control haemorrhage but, given the logistical problem of lack of a predictable donor, transplantation remains a rather limited option.

Summary

The intraoperative management of complex hepatic injuries remains a formidable challenge for the surgeon. Based on the clinical experience from large trauma centres, the evolution in management has included early mobilization of the liver and extended portal occlusion times. The preferred operative techniques are resectional debridement, hepatotomy and direct suture ligation or perihepatic packing. Deep liver sutures, anatomical resection, hepatic artery ligation and retrohepatic caval shunts have a limited, more defined, role for selected injuries. Finally, increasing emphasis has been placed on the importance of recognition and avoidance of prolonged shock, hypothermia, coagulopathy and acidosis to improve patient outcome.

Complications

Complications following liver trauma have been reported in up to 64 per cent of patients[9,35,108,125]. Associated injuries and the extent of liver injury seem to be the most important factors predisposing to postoperative problems[94,126–128]. Liver-related complications appear to be less frequent in patients managed without operation than in those managed surgically[36]. Major complications include haemorrhage, intra-abdominal abscesses, perihepatic collections of bile (bilomas) and biliary fistulas.

Haemorrhage

Rebleeding in the postoperative period is a challenging problem. Delayed haemorrhage is the most common complication of the non-operative management of hepatic injuries and is the usual indication for a delayed operation[22]. Coagulopathy, inadequate initial surgical repair and missed retrohepatic venous injury may result in further haemorrhage. Confirmed coagulation defects should be corrected as rapidly as possible with fresh frozen plasma and platelet transfusions.

Some authors recommend reoperation after transfusion of 10 units of blood in 24 h[82], but the limit of 6 units in the first 12 h seems more reasonable[3,129]. In cases with slow rebleeding when the limit of 6 units has not been exceeded, arteriography with embolization of the bleeding vessels may be helpful[21,129–135]. Failure of this technique to control haemorrhage is usually because of multiple bleeding vessels, vascular lesions distal to the area of embolization with rich collateral circulation, or bleeding from the portal or hepatic veins[134,136].

Sepsis

Intra-abdominal sepsis in the postoperative period occurs in approximately 7–12 per cent of patients[96,127]. Predisposing factors include the presence of shock and increased transfusion requirements, increased severity of liver injury, associated injuries such as small bowel or colonic perforation, the use of perihepatic packs, superficial suturing of deep lacerations with intrahepatic haematoma formation, and the presence of devitalized parenchyma[7,84,126,127,137,138]. Prophylactic antibiotics, such as cefuroxime and metronidazole, should be administered at induction of anaesthesia if laparotomy is being undertaken. Adequate initial surgical management in an effort to reduce transfusion requirements, with debridement of all devitalized tissue and early removal of perihepatic packs, has been recommended to reduce the incidence of septic complications[10,17,94,125,127,137]. If sepsis occurs, early diagnosis and aggressive treatment with drainage of any collection and appropriate intravenous antibiotic administration should be undertaken. Percutaneous transcatheter drainage has revolutionized the treatment of postoperative abscesses, and has resulted in reduced morbidity and minimal mortality rates. Surgical drainage may be indicated if there is a liver sequestrum or if percutaeous transcatheter drainage fails.

Biliary fistula

Biliary leakage following liver trauma occurs in approximately 2–8 per cent of cases[9,10,139], although a higher incidence is observed following resection for hepatic injuries[140,141]. It usually ceases spontaneously within 2 weeks of operation[10,142], but prolonged drainage of up to 3 months has been reported[143]. Factors associated with prolonged bile drainage are the presence of distal obstruction, infection and the presence of foreign body material. If the bile leak presents as a continuous discharge through a drain site, maintenance of drainage is all that is required while awaiting spontaneous resolution in most cases[9,65,139]. Endoscopic retrograde cholangiography may define the site of a bile leak and temporary stent placement may be all that is required[7]. In patients who present with an intraperitoneal bile collection (biloma), the preferred method of treatment is percutaneous drainage of the bile collection but, if this is unsuccessful, a surgical drainage procedure may be undertaken. Persistent bile fistula may require hepatic resection or a Roux-en-Y hepaticojejunostomy[139,144].

Other complications

Other complications following surgery for liver trauma are respiratory problems (in up to 40 per cent of cases)[7,35,112], wound sepsis (in up to 29 per cent of patients)[87], liver failure, hyperpyrexia (which occurs in up to 64 per cent of cases and may be due to resorption of devitalized parenchyma and hepatocellular regeneration[9]) and acalculous cholecystitis. Pancreatic, duodenal or small bowel fistulas may also develop[7]. Modern management of most of the complications of liver trauma requires a multidisciplinary approach using the combined efforts of experienced interventional radiologists, endoscopists and surgeons. Drainage of intra-abdominal abscesses or biliomas under ultrasonographic or CT guidance, and embolization of arteriovenous fistulas and bleeding vessels deep in the hepatic parenchyma, are widely used with satisfactory results, minimizing the need for a second operation[17,125].

Mortality rate

The mortality rate from liver trauma has fallen from 66 per cent in World War I, to 27 per cent in World War II, to current levels of 10–15 per cent[6,7,9,11,137,145–149]. Better knowledge of liver pathophysiology and anatomy, and enhanced resuscitation, anaesthesia and intensive care, have contributed to this improvement. The mechanism of injury has an important bearing on mortality rate with blunt trauma carrying a higher mortality rate (10–30 per cent)[44,148,150,151] than penetrating liver trauma (0–10 per cent)[7,8,35,143,152].

While most early deaths in patients with liver trauma seem to be due to uncontrolled haemorrhage and associated injuries, most late deaths result from head injuries and sepsis with multiple organ failure[94,127,153]. Other variables that may affect mortality rate are shock on admission, age above

50 years, time elapsed between accident and resuscitation, experience of the anaesthetist and surgeon, and the magnitude of surgical repair[14,128,151,154]. Since haemorrhage and sepsis are the most common causes of liver-related deaths in patients with hepatic injuries, aggressive resuscitation with prompt and expeditious haemostasis and early control of infection is paramount.

Conclusion

Optimum results for patients with severe liver trauma are obtained with a specialist team which includes an experienced liver surgeon, an anaesthetist used to dealing with the coagulopathy of liver disease, and an interventional hepatobiliary radiologist and endoscopist with expertise in managing potential postoperative complications. In addition, access to specialized equipment, such as rapid infusers, cell savers and venovenous bypass, may be required to deal with massive blood loss. Appropriate intensive care facilities are essential. Therefore, the advice for most general surgeons encountering severe liver injuries must be to consider placing perihepatic packs to control haemorrhage and to transfer the patient to a regional hepatobiliary centre for definitive management. The preferred operative treatment options of the authors involve the use of hepatotomy with direct suture ligation or resectional debridement.

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For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the October to December 1998 issues of *Der Chirurg*. A digest for the *BJS* for the same period, written by Mr Colin Johnson, appears in the German journal.

Introduction

The leading articles this quarter focus on telemedicine and ulcerative colitis in particular. Telecommunication in trauma surgery[1], teleconsultation[2], teleconference and telesurgery[3] are all reviewed in depth.

Late functional results following ileoanal pouch reconstruction in patients with ulcerative colitis are reviewed by Schumpelick and associates[4]. Herfarth *et al.*[5] review the risk of large bowel malignancy in ulcerative colitis, and the association with sclerosing cholangitis is reviewed by Heuschen *et al.*[6]. Buhr and Kroesen[7] take a critical look at typical complications associated with total proctocolectomy. Finally, Heuschen and colleagues[8] review quality of life issues after proctocolectomy for ulcerative colitis, which they also address in an original contribution[9].

Restorative proctocolectomy

Restorative proctocolectomy is widely accepted as the procedure of choice if systemic large bowel disease requires definitive treatment, because sphincter preservation avoids the creation of a permanent ileostomy. This option for treatment has made surgical therapy much more acceptable, particularly to young patients with chronic ulcerative colitis or familial polyposis of the large bowel, as they expect effective treatment of the underlying disease with minimal compromise to bowel function and quality of life. Heuschen *et al.*[9] studied postoperative morbidity, functional parameters and quality of life in 453 patients who were treated by total proctocolectomy and ileoanal pouch reconstruction at the Department of Surgery, University of Heidelberg, between 1982 and 1995. Ulcerative colitis was diagnosed in 332 patients and 121 had familial polyposis. Postoperative quality of life was studied during long-term follow-up (median follow-up 43·2 months) using the gastrointestinal quality-of-life index, a modified functional score according to Öresland and a modified Mayo Clinic activity index. The latter two were thought to mirror quality of life. One year after operation the findings in 243 patients, who had undergone J pouch reconstruction and in whom the ileostomy had been closed, revealed that neither underlying disease (ulcerative colitis, 185; familial polyposis, 58) was related to quality of life. Postoperative complications, if treated successfully, were also without effect on long-term quality of life. In contrast, patient age ($P < 0{\cdot}01$) and unsuccessful treatment of complications ($P < 0{\cdot}0001$) influenced quality of life significantly. The authors also observed a significant correlation between the functional results and quality of life. They emphasize that for patients with ulcerative colitis and familial polyposis treated by proctocolectomy with ileoanal pouch reconstruction a quality of life comparable to that of healthy individuals can be achieved only if postoperative complications are avoided or treated successfully.

For individual patients the effect of surgical treatment on quality of life is important not only in comparison with that enjoyed by a healthy person, but even more so in relation to their quality of life before operation. Obviously this starting point is quite different for patients with familial polyposis and for those with ulcerative colitis. The former are mostly free from symptoms, whereas the latter have experienced years of illness before the same operation is performed in both. Heuschen and associates[10] made a prospective comparison of quality of life before and after treatment in seven patients with familial polyposis and in 27 with ulcerative colitis selected from 602 patients treated by total proctocolectomy and ileoanal pouch reconstruction between 1992 and 1997 at the Department of Surgery, University of Heidelberg. Assessment of functional parameters, activity index and quality of life were studied before restorative proctocolectomy, before ileostomy closure and 1 year after ileostomy closure. This study confirmed poor preoperative quality of life in patients with ulcerative colitis; for these patients proctocolectomy was decisive in improving quality of life. Ileostomy closure did not result in significant further improvement. The authors observe that quality of life and activity profiles comparable to those of normal individuals were achieved in 19 patients with ulcerative colitis treated by proctocolectomy and with an uncomplicated postoperative course. If complications developed, the quality-of-life scores and activity index hardly differed from preoperative values. In contrast to ulcerative colitis, patients with familial polyposis enjoyed quality of life, activity and function similar to those of healthy individuals before operation. Proctocolectomy led to a significant reduction in quality of life and this was regained only partially by ileostomy closure.

Thymectomy for myasthenia gravis

Myasthenia gravis, with an incidence of one in 75 000, is among the few systemic diseases of presumed autoimmune origin that lend themselves occasionally to surgical treatment. Schulze and colleagues[11] from Bochum reviewed their experience of the past 5 years. A total of 11 patients with a diagnosis of symptomatic myasthenia gravis were operated on according to the referring physician's concept of early operation within 1 year of diagnosis. Median time from first symptoms to diagnosis was 4 months and that from first symptoms to operation was 8 months. One further patient underwent thymectomy for an upper mediastinal mass (suspected thymoma). All patients had extended thymectomy including removal of all fat and connective tissue in the anterior mediastinum extending upward to the lower thyroid margin. Median operating time was 102 min. Four patients were referred immediately to the normal ward after operation, seven were monitored for 1 day and another for 2 days in the intensive care unit. No perioperative mortality or long-term morbidity was recorded. Follow-up was available for 11 patients and one patient died from myocarditis shortly before a scheduled follow-up appointment. Autopsy excluded residues of thymic tissue in the anterior mediastinum. Median time to follow-up was 28 months. No patient was completely off medical treatment, but four were totally asymptomatic and a further four were considerably improved with reduced medication. No change was noted in two patients. The authors conclude that thymectomy is beneficial even in older patients and in those with purely ocular symptoms.

Pleural empyema

The incidence of pleural empyema has decreased over time, but this condition still remains a problem, and major surgical procedures may be required until cure is achieved. In a retrospective analysis Löhe and colleagues[12] identified 104 patients with complicated pleural empyema treated between 1991 and 1997 at the Department of Surgery, University of Munich. The mean(s.d.) age of the 76 men and 28 women was 54(17) (range 17–82) years. Pleural empyema was most frequently the result of pneumonia (41 per cent) or surgical manipulation (31 per cent). Perforation of the oesophagus accounted for 12 per cent of cases, adult respiratory distress syndrome (ARDS) for 9 per cent and haematogenous infection for 8 per cent. A conservative approach with chest tube drainage and antibiotic therapy alone was sufficient in 20 patients, whereas 84 patients required surgical procedures. Multiple operations were performed in 17 patients. Overall the mortality rate was 19 per cent. Mortality was highest in nine patients with ARDS (four of whom died) and in 25 patients after lung resection (eight of whom died); it was lowest after oesophageal perforation (one patient died) and pneumonia (four died). In a review of therapeutic options the authors conclude that early (within the first week) operative treatment is warranted for postsurgical empyema and an attempt at conservative therapy should be reserved for empyema associated with haematogenous infection or pneumonia.

Preoperative needle biopsy for sarcoma

Malignant soft tissue tumours often require extensive surgical procedures and may result in impaired limb function and surface mutilation, whereas benign tumours require procedures with lesser loss of function and tissue. Preoperative diagnosis is therefore fundamental to the development of optimal treatment in patients with soft tissue tumours. For larger deep-seated tumours, the concept of incisional biopsy (i.e. surgical removal of a comparatively large, at least 1 × 1 × 1 cm, block of vital tumour tissue) is currently accepted by many surgeons treating patients with soft tissue tumours. In recent years, however, needle biopsy specimens have also yielded reliable results in the hands of experienced pathologists, provided viable tumour tissue is biopsied rather than necrotic areas. The latter discrimination may be crucial for percutaneous needle biopsy. Schulte and co-workers[13] from Ulm employed colour-coded duplex ultrasonography for this purpose. The slow-flow mode was used to distinguish viable and necrotic tumour regions. The length of biopsy was between 2 and 4 cm and the needle diameter was 1·4 mm (0·8 mm for vascularized lesions). Between two and four samples were removed from the tumour through the same needle canal. For 115 malignant mesenchymal tumours (soft tissue and bone) studied by needle biopsy, the sensitivity was 96 per cent, specificity 100 per cent, accuracy 97 per cent, and positive and negative predictive values were 100 and 92 per cent respectively. The authors conclude that in their hands the results of needle biopsy were comparable to those of open biopsy and they recommend that incisional biopsy should be replaced by needle biopsy.

Ch. Herfarth
Editor
Th. Lehnert
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Original article

Intrapulmonary shunting in biliary atresia before and after living-related liver transplantation

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Background: Intrapulmonary shunting (IPS) is frequently observed and causes hypoxaemia in liver cirrhosis. This study investigated the prevalence, predictors of reversibility and the effect of living-related liver transplantation (LRLT) on IPS using contrast echocardiography in patients with end-stage biliary atresia.

Methods: Fifty consecutive patients with biliary atresia were examined for IPS using contrast echocardiography before and after LRLT until IPS disappeared. The severity of IPS was classified into five grades according to the extent of contrast in the left ventricle (0, none; 1, trivial; 2, apparent; 3, complete but less than in right ventricle; 4, as dense as in right ventricle).

Results: Thirty-two patients (grade 1, $n = 15$; grade 2, $n = 7$; grade 3, $n = 4$; grade 4, $n = 6$) had IPS before LRLT. Forty-four patients have survived for 9–26 months after LRLT. Among patients with grade 3 or 4 IPS ($n = 8$), there was a significant correlation between age at LRLT and the duration of IPS persistence after LRLT ($P = 0.044$).

Conclusion: IPS takes longer to disappear in older children than in younger ones, but always disappears eventually. LRLT is an effective treatment for biliary atresia with IPS.

Presented to the 31st annual meeting of the Pacific Association of Pediatric Surgeons, Maui, Hawaii, June 1998

Paper accepted 26 April 1999

British Journal of Surgery 1999, 86, 1139–1143

Introduction

Intrapulmonary shunting (IPS) which is caused by pulmonary vascular dilatation is frequently observed and causes hypoxaemia in liver cirrhosis including biliary atresia[1–3].

While severe hypoxia due to IPS was once considered an absolute contraindication to liver transplantation[4], it has been reported recently that several patients survived with resolution of hypoxaemia after liver transplantation[2,5–7]. However, the underlying cause and natural history of IPS remain unclear.

Contrast echocardiography provides a sensitive and reliable method for detecting IPS[3,8–11]. The prevalence of IPS, predictors of reversibility and the effect of living-related liver transplantation (LRLT) on IPS in children with end-stage biliary atresia were studied prospectively using contrast echocardiography.

Patients and methods

The subjects were 50 consecutive patients (17 boys and 33 girls) with biliary atresia aged from 6 months to 19 (mean 5·9) years who underwent LRLT between July 1996 and December 1997. All the patients had undergone Kasai procedures, but deteriorated to end-stage cirrhosis. None of these patients had intracardiac shunt, situs abnormalities or splenic malformations. Six of the 50 patients died within 2 months after LRLT. Five of six died from sepsis and one patient died from graft *versus* host disease. Fully informed consent was obtained from all the children's parents. All treatments and the study protocol were approved by the ethics committee of Kyoto University. The evaluation of IPS was based on physical examination and contrast echocardiography.

Contrast echocardiography

To visualize IPS, two-dimensional transthoracic contrast echocardiography (Sonos 500; Hewlett Packard, Andover, Massachusetts, USA) was performed in all patients before LRLT. Patients with IPS underwent contrast echocardiography 1 week after LRLT and again each month until IPS disappeared. Contrast was produced by agitating saline (3 ml saline and 0·06 ml air in patients weighing less than 20 kg, 5 ml saline and 0·1 ml air in patients weighing 20 kg or more) in two 5-ml syringes connected through a three-way stopcock. The contrast medium was administered as rapidly as possible with forceful manual injection, followed by flushing with 5–10 ml isotonic saline through a peripheral intravenous catheter in the upper limb. The progress of the contrast was observed using an apical four-chamber view. The appearance of contrast in the left ventricle three cardiac cycles after visualization of the right side of the heart was taken as evidence of IPS[8]. The severity of IPS was classified into five grades according to the extent of contrast in the left ventricle: grade 0, none; grade 1, trivial; grade 2, apparent; grade 3, complete but less than right ventricle; grade 4, as dense as in right ventricle. Examples are shown in *Fig. 1*. A negative test result was defined as no contrast detected in left heart chambers after three injections. Echocardiographic data were recorded on videotape and interpreted by two echocardiologists blinded to the clinical state of the patients. Technetium-99m-radiolabelled macroaggregated albumin (MAA) scintigraphy was performed only in patients with grade 3 or 4 IPS[12]. In patients who left this hospital, IPS was followed monthly by transcutaneous pulse oximetry until systemic arterial oxygen saturation (SaO$_2$) data returned to above 97 per cent in room air.

The results of liver function tests (serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, albumin and γ-glutamyl transpeptidase levels) 6 months after LRLT were evaluated.

Statistical analysis

Values were expressed as mean(s.d.). The relationship between variables was evaluated by linear regression analysis. Differences among groups were evaluated by one-way analysis of variance (ANOVA) with subsequent Scheffe's *post hoc* test. χ^2 test was used to evaluate sex differences. The level of significance was established as $P < 0{\cdot}05$.

Results

Forty-four patients (88 per cent) have survived with almost normal pulmonary and hepatic function 9–26 months after LRLT. Five patients died from sepsis and one patient died from graft *versus* host disease.

The mean(s.d.) levels of serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, albumin and γ-glutamyl transpeptidase 6 months after LRLT were 0·9(1·4) mg/dl, 56·0(33·3) units/l, 57·4(46·7) units/l, 4·1(0·6) g/dl and 84·4(74·0) units/l respectively.

Twenty-four of the 44 patients underwent biopsy of the liver between 5 days and 7 months after LRLT. The histological findings were acute cellular rejection in 21 patients, hepatitis in two and cholangitis in one.

Complications in 44 patients after LRLT were bile leakage in six patients, stenosis of a bile duct in five, intra-abdominal haemorrhage in two, intestinal perforation in two, herpes virus infection in two and subphrenic abscess in one.

Colour Doppler ultrasonography had shown a good flow (more than 10 ml per kg per min) in the portal vein in 43 of 44 patients. One patient, however, showed a decreased flow in to-and-fro manner just after LRLT and persisting for up to 1 month.

Thirty-two patients (11 boys; 21 girls; grade 1, $n = 15$; grade 2, $n = 7$; grade 3, $n = 4$; grade 4, $n = 6$) had positive contrast echocardiograms before LRLT (*Fig. 2*). There was no correlation between the existence of IPS and sex (χ^2 test). Median (range) partial arterial oxygen pressure (PaO$_2$) values were 100·1 (78·0–119·5) mmHg for grade 0 ($n = 14$), 101·8 (73·0–118·8) mmHg for grade 1 ($n = 8$), 93·8 (85·0–126·8) mmHg for grade 2 ($n = 4$); 58·6 (51·9–60·1) mmHg for grade 3 ($n = 3$) and 54·0 (33·3–62·2) mmHg for grade 4 ($n = 6$). There was no significant difference between PaO$_2$ values in patients with grade 0, grade 1 and grade 2 IPS or between those in patients with grade 3 and 4 IPS (ANOVA). PaO$_2$ values in patients with grade 3 or 4 IPS were significantly lower than those of patients with grade 0 IPS (both $P < 0{\cdot}0001$). The shunt ratio of grade 3 and 4 IPS calculated by MAA scintigraphy ranged from 28 to 59 (mean 40) per cent ($n = 10$).

None of the patients with grade 0, 1 or 2 IPS showed features of hypoxia. All patients with grade 3 or 4 IPS were extubated by the third day after operation and none was reintubated because of hypoxaemia or pulmonary complications.

Although serum total bilirubin values 6 months after LRLT in patients with grade 4 IPS were significantly higher than those in patients with grade 0 IPS ($P = 0{\cdot}008$), there were no significant differences in other liver function test results among the five IPS groups (ANOVA).

Eight of ten patients with grade 3 or 4 IPS survived. ABO incompatibility of donor and recipient might have affected the outcome in the two patients who died. Among the eight survivors, IPS disappeared or SaO$_2$ normalized 1–64 (mean

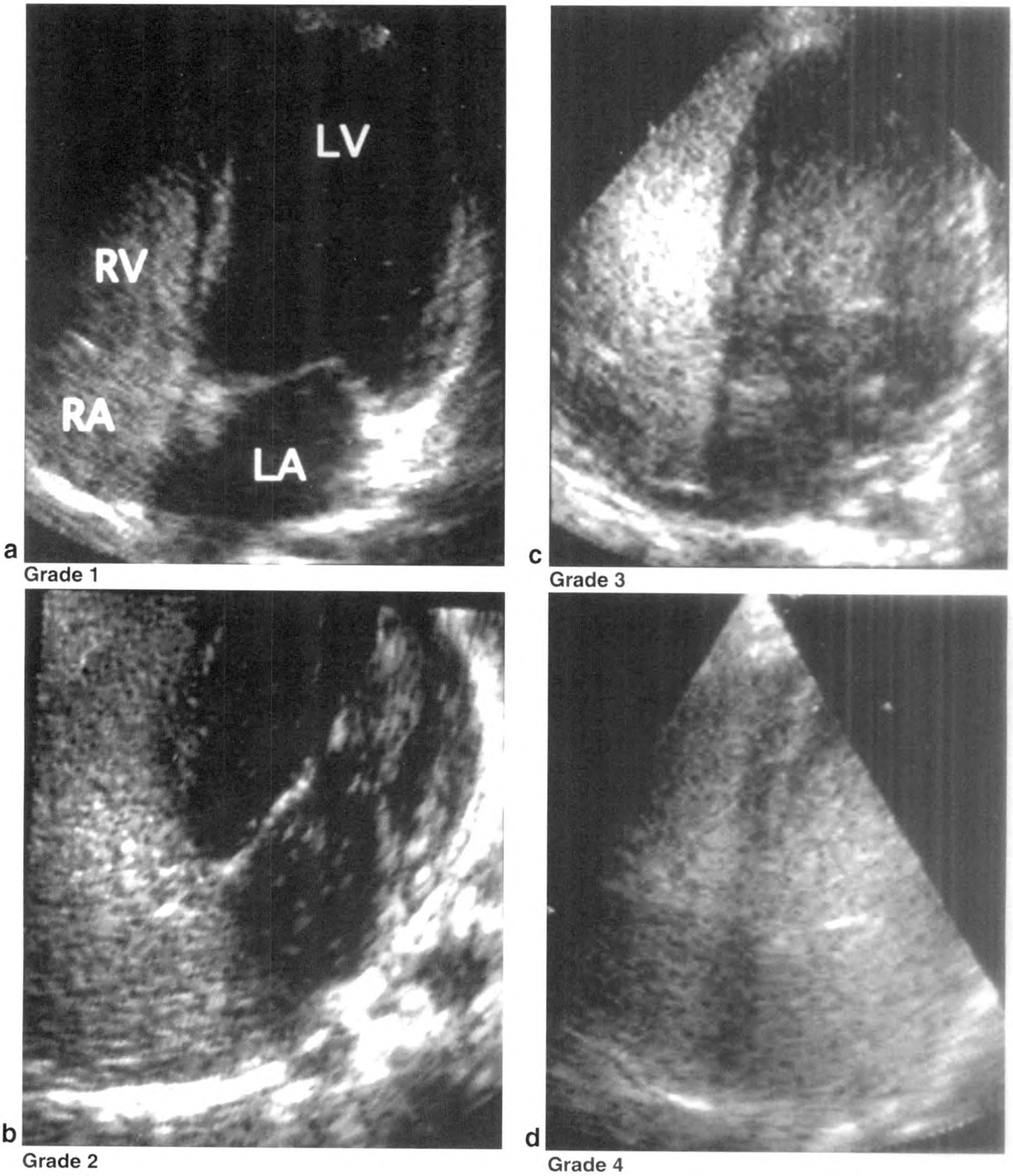

Fig. 1 Contrast echocardiography of patients with **a** grade 1, **b** grade 2, **c** grade 3 and **d** grade 4 intrapulmonary shunting. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle

22·6) weeks after LRLT. There was a significant correlation between the age at LRLT and the duration of IPS persistence after LRLT ($P = 0{\cdot}044$) (*Fig. 3*), but there was no significant correlation between the shunt ratio calculated by MAA scintigraphy before LRLT and the duration of IPS persistence after LRLT ($n = 8$, $r = 0{\cdot}571$, $P = 0{\cdot}140$).

The transplanted grafts in the eight patients were left lobe in four and lateral segment in four. The mean(s.d.) duration of IPS persistence after LRLT was 34·3(20·0) weeks in patients with a left lobe graft and 11·0(10·9) weeks in those with a lateral segment graft; there was no significant difference between the types of graft in the duration of persistence of IPS after LRLT ($P = 0{\cdot}087$, ANOVA). Donor : recipient weight ratio ranged from 0·61 to 4·02 (mean 1·51) and did not correlate significantly with the duration of IPS persistence after LRLT ($n = 8$, $r = 0{\cdot}586$, $P = 0{\cdot}127$).

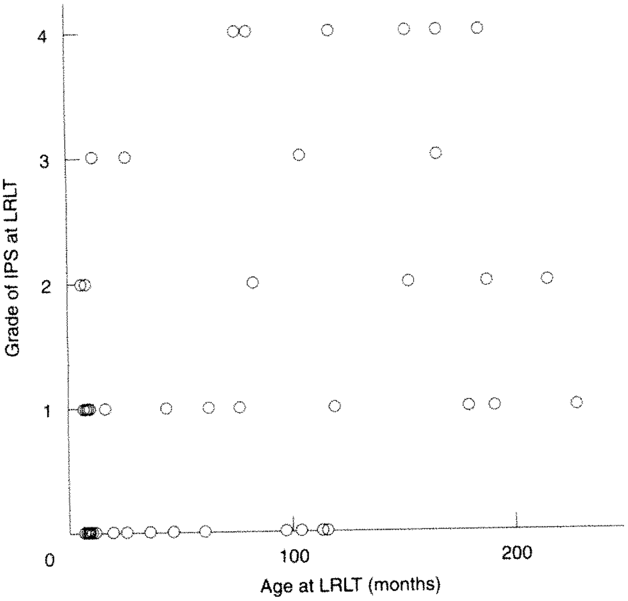

Fig. 2 Relationship between age at living-related liver transplantation (LRLT) and intrapulmonary shunting (IPS)

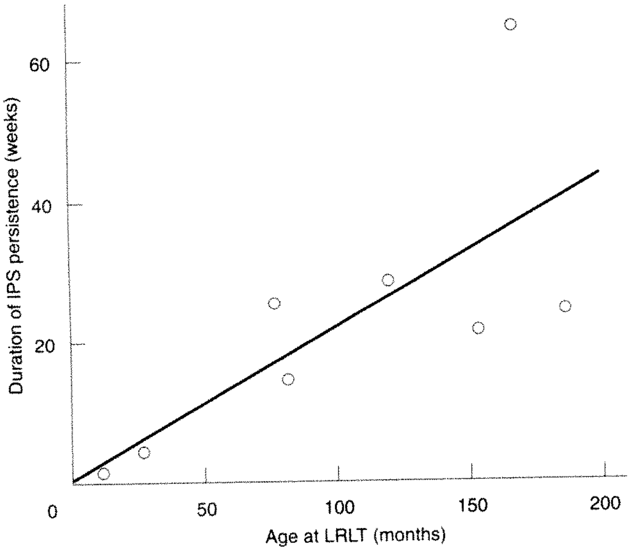

Fig. 3 Correlation between age at living-related liver transplantation (LRLT) and duration of persistence of intrapulmonary shunting (IPS) after LRLT. $r = 0{\cdot}718$, $P = 0{\cdot}044$

Discussion

Previous studies have found the prevalence of positive transthoracic contrast echocardiographic results to range from 13 to 47 per cent in adult patients with end-stage hepatic disease[3,9,10]. In this study the incidence of IPS in children with biliary atresia was 32 of 50. This rate is high relative to that in previous investigations. This may be partially explained by the fact that the present study population included many infants and young children who were relatively well visualized with transthoracic echocardiography, and that some of these patients were referred to this hospital because of hypoxaemia.

It is important to determine whether hypoxaemia is present and what causes it, since hypoxaemia may cause a high incidence of surgical complications and infection[13]. The authors consider that transcutaneous pulse oximetry is more appropriate than arterial blood gas analysis for screening hypoxaemia in infants, because it is difficult to obtain accurate arterial blood gas analysis data at rest. Periodic observation of SaO_2 data is also considered necessary in patients with biliary atresia, because it is difficult to detect cyanosis in icteric infants and it is unclear when IPS appears and progresses in severity. All patients who are suspected of cyanosis should undergo contrast echocardiography to distinguish grade 3 or 4 IPS from other pulmonary factors that decrease SaO_2.

In addition to its usefulness for screening, contrast echocardiography is a convenient and useful method of following IPS after LRLT, in infants especially, because it is difficult to perform MAA scintigraphy soon after LRLT and transcutaneous pulse oximetry data could be influenced by oxygen supply or the patient's pulmonary status. In addition, substituting contrast echocardiography for MAA scintigraphy could reduce radiation exposure to a certain extent.

Berthelot *et al.*[14] described four patients with cirrhosis who had numerous thin-walled vessels in the alveolar walls accompanied by net-like remodelling of the pleural vessels. The present observation that IPS in younger children disappeared soon after LRLT suggests that the IPS was less commonly accompanied by such remodelling. As the duration of persistence of IPS in older children was generally longer than that in infants, it is speculated that such vascular remodelling was further developed in older children and made IPS more difficult to reverse after LRLT. In a 14-year-old patient with grade 3 IPS who died, histological examination of the lung showed numerous thin-walled vessels in the alveolar walls and many tortuous pulmonary arterioles which implied remodelling.

Serum total bilirubin values in patients with grade 4 IPS were significantly higher than those in patients with grade 0 IPS 6 months after LRLT. This observation suggests that prolonged hypoxaemia hinders the recovery of liver function, because it took at least 14 weeks after LRLT for grade 4 IPS to resolve in every case.

In conclusion, the development of IPS should be detected early by careful and periodic observation with transcutaneous pulse oximetry and contrast echocardiography, which will lead to early resolution of IPS after LRLT. IPS takes longer to disappear in older children than in infants, but it always disappears eventually. LRLT is an effective treatment for biliary atresia with IPS.

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Original article

Intragraft expression of transforming growth factor β1 gene in isolated glomeruli from human renal transplants

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Background: Experimental evidence suggests that transforming growth factor (TGF) β1 is a fibrogenic cytokine. The histopathological changes of chronic renal allograft nephropathy are dominated by fibrotic changes and TGF-β may have an important aetiological role. This study investigated the relationship between intragraft TGF-β gene expression and extracellular matrix protein deposition in human renal allografts.

Methods: Sixteen cadaveric renal transplant recipients immunosuppressed with cyclosporin and steroids were studied. Individual glomeruli were isolated from protocol needle-core biopsies and, following messenger RNA extraction, intragraft gene expression was studied by reverse transcriptase–polymerase chain reaction. Collagen III deposition in these renal transplant biopsies was examined by immunohistochemistry and quantified by computerized histomorphometry.

Results: There was a positive correlation between renal cortical collagen III immunostaining and the levels of glomerular complementary DNA for TGF-β1.

Conclusion: TGF-β1 is a profibrotic influence in human renal transplants. The methods described should prove of benefit in investigating the mechanisms of chronic renal allograft damage.

Paper accepted 27 April 1999

British Journal of Surgery 1999, **86**, 1144–1148

Introduction

Chronic renal transplant rejection is one of the most important causes of late allograft loss after renal transplantation[1,2]. Although the pathophysiology of this process is complex and not completely understood, it is thought that early endothelial damage as a result of immune and ischaemic insults initiates a cascade of cytokine and growth factor production that eventually leads to graft fibrosis[3]. The histopathology of chronic rejection is dominated by neointimal hyperplasia, interstitial fibrosis and glomerulosclerosis[4]; the pathological process which links all of these features is an excess accumulation of extracellular matrix proteins[5,6].

The control of extracellular matrix turnover is multifactorial but one cytokine which seems to have a crucial fibrogenic role is transforming growth factor (TGF) β1. Following the intravenous injection of TGF-β into rodents there is marked renal and hepatic fibrosis[7]. Transfection of the TGF-β1 gene into rat kidneys directly induces glomerulosclerosis[8] and other evidence suggests a role for TGF-β in both glomerular and interstitial matrix accumulation[9–11].

Human studies have previously shown a positive correlation between TGF-β protein levels and the amount of mesangial matrix in patients with immunoglobulin A nephropathy[12] and diabetic nephropathy[13]. The aim of this study was to determine the relationship between intragraft TGF-β gene expression and extracellular matrix deposition in human renal allografts.

Patients and methods

Patients

A consecutive series of 16 patients with cadaveric renal allografts were studied. Patients were immunosuppressed with either Neoral (Sandoz Pharmaceuticals, Frimley, UK) cyclosporin (initial dose 15 mg per kg per day reducing by 2 mg per kg per week to a baseline dose of 5 mg per kg per day) or tacrolimus 0·2 mg per kg per day. Prednisolone was administered at a dose of 20 mg/day for 3 months and then reduced stepwise to a baseline dose of 10 mg on alternate days by 6 months after transplantation.

Needle-core transplant biopsies were performed under ultrasonographic guidance using a spring-loaded biopsy device[14]. All the biopsy material used in this study was taken between 3 and 24 months after transplantation at times of stable renal function. Individual glomeruli were plucked from the surface of fresh biopsy cores using ultrafine forceps under a stereoscopic microscope. Two glomeruli were usually taken from each biopsy core but individual glomeruli were analysed separately. Levels of gene expression in particular biopsies are presented as mean values derived from the data for isolated glomeruli. The remaining biopsy core was processed for routine histological examination and for immunohistochemistry.

Messenger RNA extraction and quantification[15,16]

Messenger RNA (mRNA) was extracted by immediately immersing individual glomeruli into a lysis buffer (Tris–HCl, pH 8, 100 mmol/l; lithium chloride 500 mmol/l; ethylenediamine tetra-acetic acid, pH 8, 10 mmol/l; 1 per cent lithium dodecyl sulphate; dithiothreitol 5 mmol/l; Dynal, Bromborough, UK) and incubating with proteinase K 50 μg/ml (Boehringer Mannheim, Mannheim, Germany) for 1 h at 37°C. The total mRNA extracted was purified using oligo-dT-linked Dynabeads (Dynal). These paramagnetic beads are synthesized with polythymine tails which anneal with the polyadenine tails present in all mRNA species. The glomerular mRNA is then purified by simply applying a magnet to the side of the tube and pipetting off the supernatant. Complementary DNA (cDNA) strands were synthesized for every mRNA molecule by reverse transcription (RT). This produced a stable Dynabead-linked cDNA library for each glomerulus under study. Specific cDNA molecules were amplified by polymerase chain reaction (PCR) and quantified using an enzme-linked immunosorbent assay (ELISA) (Covalink plates; Life Technologies, Paisley, UK). By using biotinylated PCR primers, each forward cDNA strand was biotinylated and captured on a biotinylated ELISA plate coated with avidin. After removal of the reverse strand, cDNA species of interest were identified by hybridization with a specific hapten-linked probe. The addition of an antihapten antibody that had been conjugated with alkaline phosphatase catalysed a colorimetric reaction in the fluid phase that was proportional to the amount of RT–PCR product in the ELISA well.

Competitive RT–PCR for glyceraldehyde phosphate dehydrogenase (GAPDH) was also used. This is an enzyme of the glycolytic pathway which is expressed constitutively in all cells. The amount of GAPDH transcript therefore correlates with the total amount of mRNA in the glomerulus and can be used to correct for differences in the cellularity of individual glomeruli, as well as differences in the efficiency of separate RT–PCR runs. A competitor cDNA template for GAPDH was constructed[16] and co-amplified with the unknown amount of native GAPDH. The competitor molecule competes with the wild type cDNA in the PCR depending upon the amount of added competitor. Previous investigation has demonstrated a linear relationship between the ratio of competitor to native signal and the amount of competitor added for levels between 5 and 90 femtomoles[16]. This allows the amount of native GAPDH in each sample to be calculated.

The expression of each gene of interest was calculated as a ratio between the amount of amplified cDNA for that gene and the amount of native GAPDH. The genes examined in this study were: collagen III, collagen IV α2 chain, matrix metalloproteinase (MMP) 2, tissue inhibitors of metalloproteinases (TIMPs) 1 and 2, tenascin and TGF-β1.

Immunohistochemistry[17]

Paraffin wax sections (3 μm) cut from renal transplant biopsies were dewaxed and treated with 6 per cent hydrogen peroxide to block endogenous peroxidase. Sections were exposed to 0·1 per cent trypsin (Difco, Cowley, UK) in 0·12 per cent calcium chloride, pH 7·8, for 25 min at 37°C. A standard indirect immunoperoxidase method was used with a primary antibody to type III collagen (Europath, Bude, UK) applied overnight at 4°C. A counterstain was omitted in order to facilitate subsequent image analysis.

Image analysis

Sections were viewed on a Zeiss photomicroscope III (Oberkochen, Germany) with a video camera attachment. The camera was linked to the in-built framegrabber board of an Apple Macintosh microcomputer (Cupertino, California, USA), and the histological images were imported directly to the freeware image analysis programme NIH-Image (US National Institutes of Health; www.rsb.info.nih.gov/nih-image/). Sequential greyscale images of renal cortex were captured using the × 10 objective, moving along the central line of each biopsy specimen from one end of the available cortex to the other, without overlapping. To calculate the area fraction of collagen III immunostaining, a threshold was applied to each image at a constant level which distinguished between the stained component (rendered black) and the unstained background (rendered white). The proportion of black to white pixels in the image was then calculated as a percentage. This represents the percentage volume fraction of the tissue which is occupied by the stained element[18]. A set of macros was written to automate this process, such that sequential fields could be measured with just two keystrokes per field. All measurements were performed by the same investigator (G.B.) who was blinded to the graft outcome data. The method has been validated previously using a larger sample of renal allograft biopsy material[17].

Statistical analysis

The levels of expression of different genes measured by RT–PCR were correlated with each other and with the level of collagen III immunostaining. Spearman's rank correlation coefficients and their associated P values were calculated using Instat 1.12 (Graph-Pad Software, San Diego, California, USA). $P < 0{\cdot}05$ was considered significant.

Results

The relationships between different cDNA species from isolated glomeruli are shown in *Table 1*. TGF-β1 expression was detected in all the glomeruli studied and statistically significant positive correlations were found between the cDNA levels for TGF-β1 and cDNA levels for MMP-2 ($r_S = 0{\cdot}878$), TIMP-1 ($r_S = 0{\cdot}652$), TIMP-2 ($r_S = 0{\cdot}705$) and tenascin ($r_S = 0{\cdot}893$). No significant relationship was found between glomerular TGF-β1 cDNA and glomerular collagen III or IV cDNAs. *Table 2* shows the correlations between the level of collagen III protein measured by image

Table 1 Correlation between level of complementary DNA for transforming growth factor β1 and other complementary DNA species in isolated transplant glomeruli ($n = 20$)

cDNA species	r_S	P
TGF-β *versus* collagen III	0·290	n.s.
TGF-β *versus* collagen IV α2	0·374	n.s.
TGF-β *versus* MMP-2	0·878	< 0·01
TGF-β *versus* TIMP-1	0·652	< 0·02
TGF-β *versus* TIMP-2	0·705	< 0·02
TGF-β *versus* tenascin	0·893	< 0·01

cDNA, Complementary DNA; TGF, transforming growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; n.s., not significant

Table 2 Correlations between level of collagen III immunostained protein and complementary DNA species in isolated transplant glomeruli ($n = 20$)

Comparison	r_S	P
Collagen III protein *versus* collagen III cDNA	0·626	< 0·02
Collagen III protein *versus* collagen IV α2 cDNA	0·145	n.s.
Collagen III protein *versus* MMP-2 cDNA	0·105	n.s.
Collagen III protein *versus* TIMP-1 cDNA	0·430	0·1
Collagen III protein *versus* TIMP-2 cDNA	0·835	< 0·01
Collagen III protein *versus* tenascin cDNA	0·200	n.s.
Collagen III protein *versus* TGF-β cDNA	0·704	< 0·01

cDNA, Complementary DNA; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; TGF, transforming growth factor; n.s., not significant

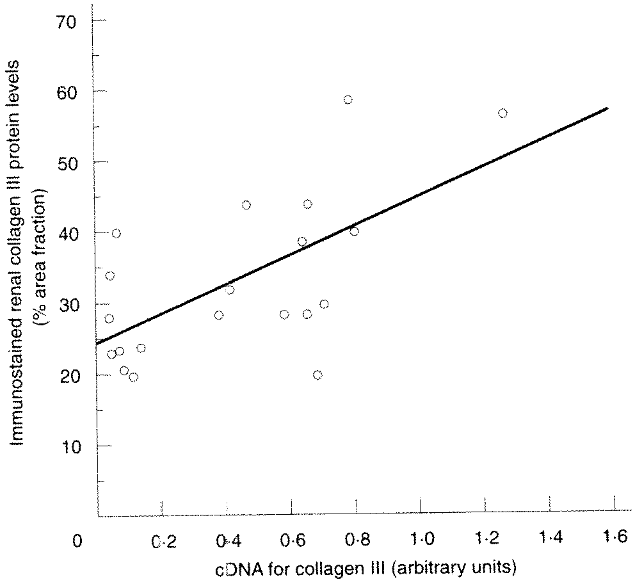

Fig. 1 Relationship between collagen III protein level and glomerular collagen III complementary DNA (cDNA) in human renal allografts. $r_s = 0{\cdot}626$, $P < 0{\cdot}02$

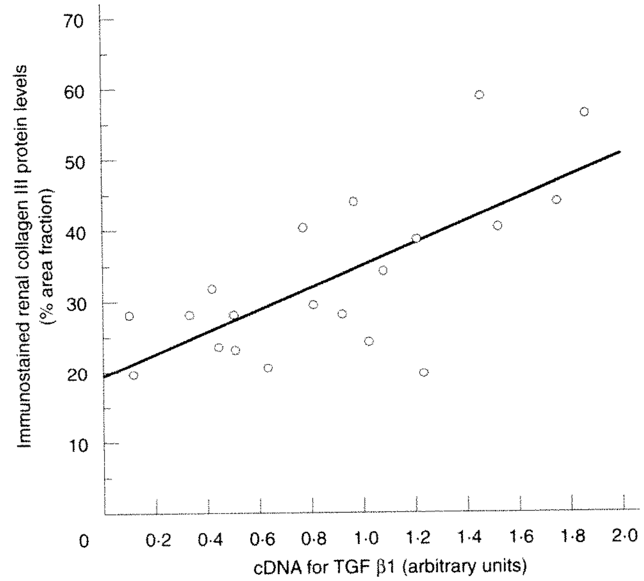

Fig. 2 Relationship between collagen III protein level and glomerular complementary DNA (cDNA) for transforming growth factor (TGF) β1 in human renal allografts. $r_s = 0{\cdot}704$, $P < 0{\cdot}01$

analysis of immunostained sections and the various glomerular cDNAs measured by RT–PCR–ELISA. There was a reasonably strong positive correlation between the level of collagen III protein expression in the renal cortex as a whole (glomeruli and tubulo–interstitium) and collagen III cDNA levels in the glomeruli (*Fig. 1*). In addition, strong positive correlations were found between collagen III protein deposition in the renal cortex and glomerular TGF-β1 cDNA (*Fig. 2*) as well as between collagen III protein levels and glomerular TIMP-2 cDNA.

Discussion

This preliminary study is the first demonstration of the relationship between the expression of mRNA encoding TGF-β1 in isolated glomeruli taken from human renal transplant biopsies and the degree of interstitial fibrosis in the same tissue. It has already been reported that normal glomeruli express detectable but low levels of TGF-β[19] but the data presented here suggest that glomerular TGF-β1 is a profibrotic influence in human renal transplants. This supports the findings of Sharma *et al.*[20] who showed that intragraft expression of mRNA for TGF-β1 was significantly correlated with interstitial fibrosis and chronic allograft nephropathy. Their study recorded TGF-β1 expression and allograft fibrosis as either present or absent and correlated these features using simple contingency tables rather than the quantitative methods used here. Moreover, Sharma *et al.*[20] extracted total mRNA from renal transplant biopsies which were performed for allograft dysfunction rather than the protocol biopsies which were used in the present work. In view of these considerations the present study provides a unique insight into the role of TGF-β in the development of chronic allograft rejection.

Glomerular haemodynamic factors are known to be important determinants of progressive renal disease in native and transplanted kidneys[21,22]. Nephron loss as a result of ischaemia and acute rejection results in adaptive changes in the surviving nephrons, causing glomerular injury and ultimately glomerulosclerosis; this was the reason for examining gene expression in individual glomeruli. None the less, fibrosis in the renal interstitium correlates best with renal function[23,24] and this was the justification for measuring interstitial fibrosis by immunohistochemistry.

The process of extracellular matrix remodelling is of considerable complexity, being determined by a balance between the rate of matrix synthesis and the rate of its degradation[5]. Extracellular matrix is remodelled continuously and its degradation is controlled by proteolytic MMPs; these in turn are regulated by their own tissue inhibitors (TIMPs). That cDNA for TGF-β was correlated with cDNA for MMP-2 and the TIMPs is of interest, but to fully understand the role of TGF-β, the balance of these opposing forces must be determined.

Although RT–PCR is the best available method for studying the rate of synthesis of extracellular matrix components, the assumption usually made is that the changes described are carried through to the protein level. In this study the findings at the gene expression level have been correlated with protein deposition measured by quantitative immunohistochemistry. The positive correlation between the level of TGF-β transcripts and collagen III immunostaining suggests that TGF-β is a fibrogenic influence but does not explain its mechanism of action. TGF-β may act by increasing the synthesis of matrix proteins such as the collagens or alternatively it may inhibit the removal of the same proteins; this latter action could either be direct, by inhibiting the expression of MMPs, or indirect, by increasing the production of TIMPs. The positive correlation between cDNA levels for both TIMPs and the amount of immunostained collagen III protein suggests that inhibition of collagen degradation is the more important. This is, however, only one possible hypothesis. Another explanation is that there may be asynchronous changes in TGF-β transcript expression and collagen gene transcript expression.

Tenascin is a glycoprotein which appears to be produced when matrix remodelling is active and may reflect new fibrosis rather than old scarring[25]. Although the expression of TGF-β and tenascin were positively correlated, a strong relationship between tenascin mRNA and collagen III protein levels could not be demonstrated.

This study involved only a relatively small number of renal transplant recipients and the findings should be regarded as preliminary. The patients were immunosuppressed with two different primary drug regimens (cyclosporin or tacrolimus) and the effects of these and other influences such as donor factors will only be determined by further study. None the less, the RT–PCR and immunohistochemical techniques described should prove to be useful tools in the investigation of chronic renal allograft damage and may provide sensitive measures of the efficacy of different treatment strategies.

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Original article

Assessment of lower extremity venous function using foot venous pressure measurement

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Background: Measurement of foot venous pressure (FVP) is useful for evaluating chronic venous insufficiency (CVI) functionally, because CVI always causes venous hypertension. In the present study, the various FVP parameters were analysed according to the new classification of venous disorders based on clinical, aetiological, anatomical and pathophysiological data (the CEAP classification).
Methods: During the past 7 years, a total of 257 legs in 196 consecutive patients with CVI have been studied. The following FVP parameters were assessed: the percentage decrease in pressure from rest with manual calf compression, the rate of increase of pressure during 4 s after compression (4SR) and the time to 50 per cent recovery of pressure (RT_{50}) after release of compression.
Results: The incidence of skin changes due to venous stasis increased as the percentage pressure drop and RT_{50} fell. In addition, a pressure drop of less than 72 per cent and an RT_{50} of less than 20 s could detect legs with skin changes with a sensitivity of 76 per cent and a specificity of 62 per cent. In legs with primary varicose veins, pressure drop, 4SR and RT_{50} values deteriorated in proportion to the severity of the associated deep venous reflux.
Conclusion: FVP parameters correlate well with the severity of clinical manifestations and venous reflux, and could be used quantitatively to evaluate the severity of CVI.

Paper accepted 16 May 1999

British Journal of Surgery 1999, 86, 1149–1154

Introduction

A classification of chronic venous insufficiency (CVI) was proposed by an International Consensus Committee associated with the American Venous Forum in 1995[1]. This classification was based on Clinical, Etiologic, Anatomic and Pathophysiologic data (CEAP), and allowed a more accurate description of CVI as well as uniform reporting of data[2,3].

Several techniques have been available for quantitative evaluation of CVI, including duplex imaging, strain gauge plethysmography and air plethysmography[3–5]. Ambulatory venous pressure (AVP) has been the traditional 'gold standard' for evaluating CVI, because venous insufficiency is caused by venous hypertension[6–17].

In this study, the relationship between foot venous pressure (FVP) parameters and the CEAP classification was compared in patients with CVI.

Patients and methods

From January 1991 to December 1997, a total of 257 legs of 196 consecutive patients with CVI were studied. The patients comprised 70 men and 126 women of mean age 57 (range 19–80) years. The clinical features of CVI were assessed according to the CEAP classification of the American Venous Forum[1] (*Table 1*).

Phlebography

Ascending phlebography was performed, using a 21-G butterfly needle inserted into the medial digital vein of the great toe, on all limbs to evaluate the entire venous system. In 50 legs, the deep venous system was not visualized clearly, so direct phlebography was performed[18]. For direct phlebography, the common femoral vein was punctured in the downward direction with a 14-G polytetrafluoroethylene catheter. After retrograde insertion of the guidewire across the venous valves into the deep veins, a 4-Fr catheter was introduced over the guidewire and 15–20 ml of low osmolar contrast medium was injected directly into the deep veins. With this technique, clear visualization of the deep venous system and a definite diagnosis of incompetent perforating veins were obtained in all legs. Descending phlebography, using a long 20-G needle inserted into the common femoral vein, was performed with the aid of a Valsalva manoeuvre on 217 legs to evaluate deep venous reflux[19,20].

Table 1 Classification of chronic venous disease[1]

Clinical classification	
Class 0	No visible or palpable signs of venous disease
Class 1	Telangiectasia or reticular veins, malleolar flare
Class 2	Varicose veins
Class 3	Edema without skin changes
Class 4	Skin changes ascribed to venous disease (e.g. pigmentation, venous eczema, lipodermatosclerosis)
Class 5	Skin changes as defined above with healed ulceration
Class 6	Skin changes as defined above with active ulceration
Etiologic classification	
Congenital (Ec)	Cause of the chronic venous disease present since birth
Primary (Ep)	Chronic venous disease of undetermined cause
Secondary (Es)	Chronic venous disease with an associated known cause (post-thrombotic post-traumatic, other)
Pathophysiologic classification	
Reflux (P_R)	
Obstruction (P_O)	
Reflux and obstruction ($P_{R,O}$)	
Anatomic classification	
Segment no.	
Superficial veins (A s 1–5)	
1	Telangiectasias/reticular veins
	Greater (long) saphenous veins
2	Above-knee
3	Below knee
4	Lesser (short) saphenous vein
5	Non-saphenous
Deep veins (A d 6–16)	
6	Inferior vena cava
	Iliac
7	Common
8	Internal
9	External
10	Pelvic: gonadal, broad ligament
	Femoral
11	Common
12	Deep
13	Superficial
14	Popliteal
15	Tibial (anterior, posterior or peroneal)
16	Muscular (gastrocnemial, soleal, other)
Perforating veins (A p 17, 18)	
17	Thigh
18	Calf

Foot venous pressure measurement (*Fig. 1*)

All legs underwent FVP measurement using the following method[16]. The 21-G butterfly needle for ascending phlebography was connected to a transducer (TP-400T; Nihon Kohden, Tokyo, Japan) for continuous recording of FVP. Resting pressure was measured with the patient standing on the contralateral leg with the knee joint of the ipsilateral leg slightly flexed. The calf was then compressed manually ten to 12 times. As a result, the venous pressure decreased to a plateau, defined as the postcompression venous pressure (PCVP). The percentage decrease in pressure was calculated as follows: resting pressure − PCVP/resting pressure. During the increase in pressure after release of compression, the following parameters were measured: the pressure at 4 s after release of compression (4SP), the rate of increase of pressure during the initial 4 s (4SR = (4SP − PCVP)/(resting pressure − PCVP), and the time for 50 per cent recovery of pressure from PCVP (RT_{50}). After two narrow rubber tourniquets had been placed around the upper thigh and above the knee to occlude the superficial veins, the measurements were repeated. When diagnosed, occlusion of the superficial veins and patency of the deep veins were confirmed by duplex imaging. FVP data were compared with the clinical manifestations and the severity of deep venous reflux according to the CEAP classification.

Fourteen legs in healthy volunteers of mean age 28 (range 25–32) years with no clinical evidence of venous problems or varicose veins were used as the control. These legs were also defined by duplex imaging as having no venous disorders such as venous reflux, thrombosis or anomaly.

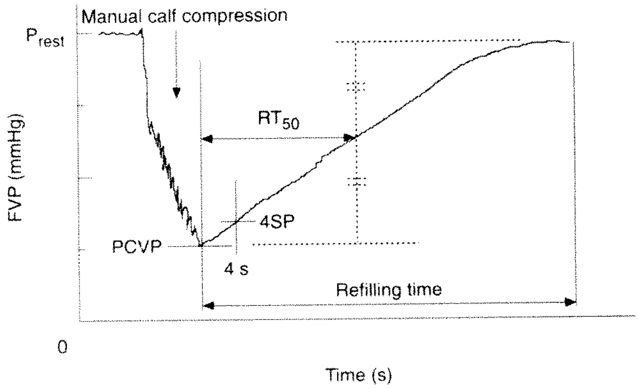

Fig. 1 Foot venous pressure (FVP) measurement. P_{rest}, resting pressure; PCVP, postcompression venous pressure (= ambulatory venous pressure); pressure drop = (P_{rest} − PCVP)/(P_{rest}); 4SP, the pressure 4 s after release of compression; 4SR = (4SP − PCVP)/(P_{rest} − PCVP); RT_{50}, time for 50 per cent recovery of pressure from PCVP; === indicates equality

The mean(s.d.) values obtained from the control group were: PCVP 25(5) mmHg, pressure drop 72(5) per cent, 4SR 13(8) per cent and RT_{50} 20(11) s.

Statistical analysis

Data are expressed as mean(s.d.). Statistical analysis was carried out with *post hoc* testing by Scheffe's *F* test; $P < 0.05$ was considered significant.

Results

Clinical classification (*Table 1*)

There were 12 legs in class 1, 159 in class 2, 12 in class 3, 49 in class 4, five in class 5 and 20 in class 6.

Aetiological classification

Eight legs had a congenital, 210 a primary and 39 a secondary venous disorder. The congenital group included Klippel–Trenaunay syndrome (six legs) and venous dysplasia (two legs). The secondary venous disorders included deep venous thrombosis without recanalization (12 legs) deep venous thrombosis with partial recanalization (26 legs) and superficial venous thrombosis (one leg).

Anatomical and pathophysiological classification

A total of 176 legs with primary varicose veins (Ep) were classified into three groups according to the severity of associated deep venous reflux shown by descending phlebography: group 1 (73 legs), superficial reflux only (Ep, As, P 2, 3, r); group 2 (73 legs), superficial reflux and mild deep venous reflux (Ep, As, d, P 2, 3, 13, r); group 3 (30 legs), superficial reflux and severe deep venous reflux (Ep, As, d, P 2, 3, 13, 14, r).

Relationship between skin changes and foot venous pressure parameters

On the basis of the percentage pressure drop and RT_{50} values obtained from the control group (mean 72 per cent and 20 s respectively), all legs were divided into four categories. The incidence of skin changes due to venous stasis was 44 per cent (56 of 126) when the pressure drop was lower than 72 per cent and RT_{50} was shorter than 20 s (*Fig. 2*). An increasing prevalence of skin changes was associated with lower values of percentage pressure drop and RT_{50}. In addition, a pressure drop of less than 72 per cent and an RT_{50} lower than 20 s detected legs with skin changes with a sensitivity of 76 per cent and a specificity of 62 per cent.

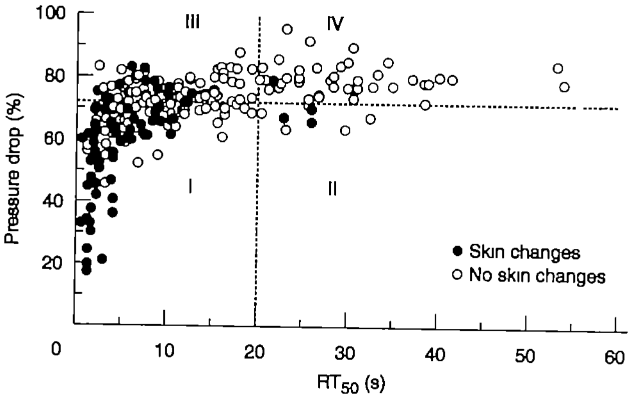

Fig. 2 Incidence of skin change according to values for the percentage decrease in foot venous pressure (pressure drop) and the time for 50 per cent recovery from postcompression venous pressure (RT_{50}), divided into four areas. I, 56 (44 per cent) of 126 legs had skin changes; II, three of eight legs; III, 14 (16 per cent) of 85 legs; IV, one of 38 legs. The dotted lines shown mean control values of 72 per cent for pressure drop and 20 s for RT_{50}

Comparison of foot venous pressure parameters and clinical classification

Using stratification on the basis of skin changes, the CEAP clinical group comprising classes 1–3 ($n = 183$) was compared with that comprising classes 4–6 ($n = 74$). Legs of patients in classes 4–6 showed a significantly lower percentage pressure drop, higher 4SR and shorter RT_{50} than those in classes 1–3 and in controls. In contrast, there were no significant differences between the group comprising classes 1–3 and the control group with respect to percentage pressure drop and 4SR (*Fig. 3*).

Comparison of foot pressure drop parameters and aetiological classification

Six legs of patients with Klippel–Trenaunay syndrome showed significantly lower values for percentage pressure drop compared with legs of patients with primary venous disease. In addition, there were significant differences between primary and secondary groups in the values for percentage pressure drop and 4SR (*Fig. 4*). In contrast, in the secondary group no significant differences were seen between deep venous thrombosis with partial recanalization and without recanalization in the percentage pressure drop, 4SR and RT_{50} values (data not shown).

Comparison of foot venous pressure parameters with anatomical and pathophysiological classifications

The values for pressure drop, 4SR and RT_{50} were significantly worse in group 2 (Ep, As, d, P 2, 3, 13, r) and group 3 (Ep, As, d, P 2, 3, 13, 14, r) than in group 1 (Ep, As, P 2, 3, r). The 4SR value was significantly different between groups 2 and 3 (*Fig. 5*). When tourniquets were applied, values for pressure drop, 4SR and RT_{50} were significantly improved in all groups. As a result, there were no significant differences between groups 1 and 2, with the exception of RT_{50}. However, 4SR and RT_{50} remained significantly different in group 3 compared with the other two groups (data not shown).

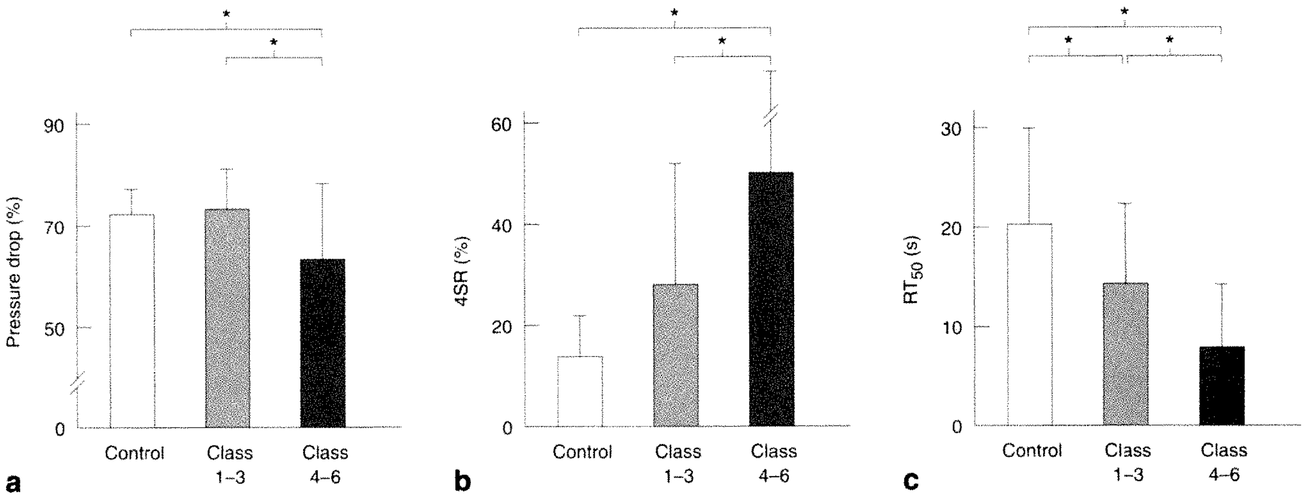

Fig. 3 Comparison of foot venous pressure (FVP) parameters and the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) clinical classification:

a percentage decrease in FVP;

b rate of increase in FVP during the first 4 s after compression (4SR);

c time for 50 per cent recovery from postcompression venous pressure (RT_{50}).

Values are means(s.d.). $^*P < 0.01$ (Scheffe's F test)

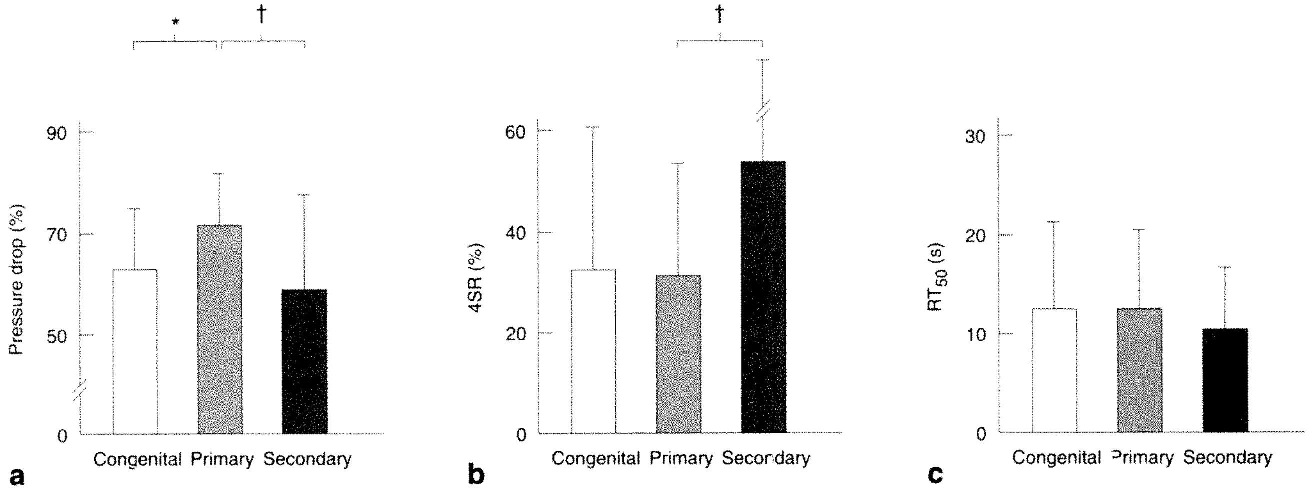

Fig. 4 Comparison of foot venous pressure (FVP) parameters and the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) aetiological classification:

a percentage decrease in FVP;

b rate of increase in FVP during the first 4 s after compression (4SR);

c time for 50 per cent recovery from postcompression venous pressure (RT_{50}).

Congenital disorder (Klippel–Trenaunay syndrome), $n = 6$; primary disorder, $n = 210$; secondary disorder, $n = 39$. Values are means(s.d.). $^*P < 0.05$, $^\dagger P < 0.01$ (Scheffe's F test)

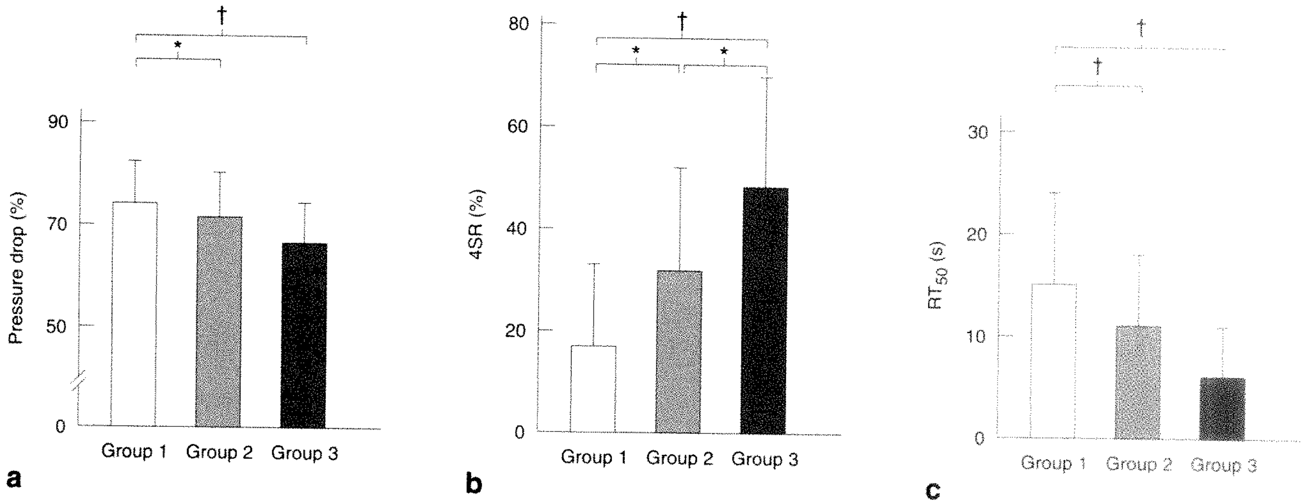

Fig. 5 Comparison of foot venous pressure (FVP) parameters with anatomical and pathophysiological classifications:
a percentage decrease in FVP;
b rate of increase in FVP during the first 4 s after compression (4SR);
c time for 50 per cent recovery from postcompression venous pressure (RT$_{50}$).
Group 1, Ep, As, P 2, 3, r; group 2, Ep, As, d, P 2, 3, 13, r; group 3, Ep, As, d, P 2, 3, 13, 14, r. Values are mean(s.d.). $^*P<0.05$, $^†P<0.01$ (Scheffe's F test)

Discussion

In this hospital CVI is usually assessed by means of plethysmography, duplex imaging, air plethysmography and FVP measurement. It is difficult to obtain objective analysis of the whole venous system because of its complexity. For quantitative functional evaluation of CVI, FVP measurement has become the first choice because the severity of CVI is related to the degree of venous stasis. Generally, AVP has been considered the 'gold standard' for evaluating CVI because venous hypertension is the main cause of stasis ulceration[7–10]. However, some investigators have noted the lack of a consistent relationship between ambulatory venous hypertension and stasis ulcer; others have stated that the FVP reflects the severity of venous abnormalities but does not predict the extent of the associated lesions[7–9,12–14]. AVP alone does not provide sufficient information on venous haemodynamics, whereas the various FVP parameters could be used to assess the severity of CVI more accurately[11,16].

FVP can be measured during tip-toe exercise or manual calf compression. The tip-toe exercise reflects the physiological response more closely than manual calf compression. However, the authors' previous study, as well as that of Raju[17], demonstrated that manual calf compression has a higher reproducibility than the tip-toe exercise because the latter often causes extravasation. The AVP value obtained from manual calf compression should be termed the PCVP. In a previous study[11] it was shown that PCVP reflected a patient's height; therefore the percentage pressure drop derived from the PCVP is a more sensitive venous measurement. When venous valve insufficiency is severe on descending phlebography, the contrast can reach the calf within a few seconds through the superficial and/or deep veins. From the photoplethysmographic data of Sarin *et al.*[21], a non-linear curve was obtained for venous refilling assessed by FVP, showing a different gradient for FVP recovery between early and late phases after exercise. This indicates that rapid venous refilling, represented by the values of 4SR and RT$_{50}$, has the greatest influence on development of the stasis syndrome in CVI. In the present study, a higher incidence of skin change due to venous stasis was associated with a lower percentage pressure drop, a higher 4SR value and a shorter RT$_{50}$.

Regarding the aetiological classification, secondary venous disorders gave significantly worse values for percentage pressure drop and 4SR compared with the primary group. Following deep venous thrombosis there was a higher resistance to venous outflow and therefore a higher AVP. However, in secondary venous thrombosis there was no significant difference between deep venous thrombosis with partial recanalization and without recanalization. In the aetiologial classification, FVP parameters have been as useful as duplex imaging and phlebography.

With respect to the anatomical and pathophysiological classifications, the percentage pressure drop, 4SR and RT$_{50}$

alues were significantly worse in legs with deep venous eflux (As, d, P 13 and/or 14, r) than in those without reflux As, Pr). However, there were no significant differences etween veins with above-knee reflux (Ep, As, d, P 2, 3, 13, r) nd those with below-knee reflux (Ep, As, d, P 2, 3, 13, 14, r), ith the exception of the 4SR value. Legs with superficial enous reflux also often had deep venous reflux. When ourniquets were placed on the upper thigh and above the nee to exclude the influence of superficial venous reflux, he values for percentage pressure drop, 4SR and RT_{50} were ignificantly improved in all legs. In legs with below-knee eflux, 4SR and RT_{50} remained significantly worse, which night suggest that this group could be targeted to benefit rom deep venous valve reconstruction[22,23].

In summary, a lower percentage pressure drop on FVP neasurement indicates resistance to venous return, such as leep venous thrombosis, and a shorter RT_{50} or higher 4SR alue indicates rapid refilling in the venous system. Tourniquets can be used to diagnose significant deep enous reflux. The sensitivity and specificity of FVP parameters were inadequate to distinguish variation in the CEAP classification[9,24]. However, FVP measurement was useful for evaluating venous function; it is simple and cost effective, and could become an important method for classifying venous dysfunction.

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Prevalence of aortic aneurysm in men with a history of inguinal hernia repair

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Background: Population-based screening for abdominal aortic aneurysm (AAA) is still a subject of debate. This study examined whether subjects with a history of inguinal hernia were at increased risk sufficient to justify screening.

Methods: The prevalence of AAA was documented in 156 men aged 55 years and older, discharged after inguinal hernia surgery, and compared with the prevalence in 1771 men without a history of inguinal hernia who were participating in a screening survey for AAA. The influence of age and smoking status was assessed.

Results: The prevalence of AAA in men with a history of inguinal hernia was 12·2 (95 per cent confidence interval (c.i.) 7·0–17·4) per cent and 3·7 (95 per cent c.i. 2·8–4·6) per cent in those without such a history; prevalence ratio 3·3 (95 per cent c.i. 2·0–5·3). In current smokers the prevalence of abdominal aneurysm was 4·2 (95 per cent c.i. 2·1–8·2) times higher in those with compared with those without a history of inguinal hernia. In non-smokers the prevalence ratio was 1·9 (95 per cent c.i. 0·5–7·0).

Conclusion: Men with a history of inguinal hernia are at increased risk of AAA, most notably if they are cigarette smokers. Ultrasonographic screening could be considered before operation for inguinal hernia.

Paper accepted 15 May 1999

British Journal of Surgery 1999, 86, 1155–1158

Introduction

Aneurysms of the abdominal aorta are an important and preventable cause of death[1]. The prevalence of aneurysm ranges from 1 per cent in men aged 55–60 years to 10 per cent in those 80 years and older[2], and has increased in recent decades[3].

Early detection and surgical treatment may prevent death from rupture. The cost-effectiveness of population-based screening for this condition is still a matter of debate[4], but screening subjects at increased risk may be less costly: the number of subjects who require screening is lower and the proportion of aneurysms detected may be acceptable.

Several high-risk groups have already been identified, including smokers[5], patients with hypertension[6] or peripheral arterial obstructive disease[7], or relatives of patients with an abdominal aortic aneurysm (AAA)[8]. An increased prevalence of AAA has also been demonstrated in patients with pulmonary emphysema[9]. In addition, an increased prevalence of inguinal hernia has been reported in patients with an AAA[10].

The relation between emphysema, inguinal hernia and aneurysms of the abdominal aorta may be attributable to systemic elastin and collagen fibre degeneration[11]. This process of fibre degeneration is thought to be enhanced by smoking[12].

The present study compared the prevalence of AAA in men aged 55 years or more with, and without, a history of inguinal hernia.

Patients and methods

All the records of 261 men aged 55 years or older who were discharged after operation for an inguinal hernia from the Department of Surgery of Ruwaard van Putten Hospital in Spijkenisse, the Netherlands, between 1990 and 1996 were examined. Their general practitioners were interviewed by telephone to check whether the patient was still alive and healthy enough to participate in the study. Patients were first invited by letter and later by telephone to participate in the study. Of all patients, 20 (7·7 per cent) had died; in none of these was AAA rupture the cause of death, according to the general practitioner. A further 40 (15·3 per cent) had moved to a nursing home and could not be enrolled. Of the remainder, 45 (22·4 per cent) did not participate, mainly because the general practitioner thought they were too ill to take part. Ultimately, 156 of those we contacted (77·6 per cent) agreed to participate. All patients visited the hospital where an interview, physical examination and ultrasonographic examination of the abdominal aorta were performed by an experienced physician.

A reference group was selected from 2217 men aged 55 years or older who underwent ultrasonographic examination of the abdominal aorta as part of the Rotterdam Elderly Study[13]. A trained research assistant interviewed all participants at home. A history of inguinal hernia was established during the interview, and was considered to be present when operation for this condition had been carried out. No additional information was obtained. In 446 men (20·1 per cent) a history of inguinal hernia was reported during the interview and these men were excluded from the reference group.

All subjects (men with an inguinal hernia from Ruwaard van Putten Hospital as well as the Rotterdam Study participants) had ultrasonography. The presence of cardiovascular risk factors and disease were assessed by a research physician using standard methods and definitions[14].

Ultrasonography of the abdominal aorta was performed with a 3·5-MHz linear array probe: an Aloka SSD 620 (Aloka, Tokyo, Japan) for men with inguinal hernia and a Toshiba SSH 60A (Toshiba American Medical Systems, Tustin, California, USA) for those in the Rotterdam Study. All patients were in the supine position, according to the Rotterdam Study scanning protocol[15]. An AAA was considered to be present when the distal diameter of the abdominal aorta was 35 mm or more, or the diameter of the distal aorta was at least 50 per cent larger than that of the proximal aorta.

The χ^2 test was used to compare differences between binominal variables in two groups; differences between continuous variables were tested with Student's *t* test. Prevalence and prevalence ratios of abdominal aneurysms were estimated with 95 per cent confidence intervals (c.i.) for those who had, or had not, undergone operation for inguinal hernia. Prevalence and prevalence ratios with 95 per cent c.i. were also estimated in subgroups of patients according to age and smoking behaviour.

Results

Men with a history of inguinal hernia repair were relatively older and had a more unfavourable cardiovascular risk profile than those without (*Table 1*).

The mean distal aortic diameter in men with a history of inguinal hernia surgery was 21·9 (95 per cent c.i. 20·3–23·5) mm, and was higher than that in the reference group (19·6 (95 per cent c.i. 19·3–19·8) mm). The mean proximal aortic diameter in those with a previous inguinal hernia (20·9 (95 per cent c.i. 20·0–22·0) mm) was comparable to that in the reference group (21·0 (95 per cent c.i. 20·8–21·1) mm).

In 12·2 (95 per cent c.i. 7·0–17·4) per cent of men with a history of inguinal hernia, an aortic aneurysm was present, compared with 3·7 (95 per cent c.i. 2·8–4·6) per cent in those without such a history; the prevalence ratio was 3·3 (95 per cent c.i. 2·0–5·3). The prevalence of AAA increased with age in all age groups but was consistently higher for those with a history of inguinal hernia (*Table 2*).

Table 1 Baseline characteristics of 156 men with a history of inguinal hernia and 1771 men from the Rotterdam Elderly Study with no such history

	History of inguinal hernia repair	No history of inguinal hernia	*P**
Mean(s.d.) age (years)	69·4(7·1)	66·3(7·3)	<0·001
Mean(s.d.) blood pressure (mmHg)			
Systolic	143(19)	138(22)	<0·05
Diastolic	83(10)	75(11)	<0·001
Never smoked (%)	35	15	<0·001
Former smoker (%)	40	60	<0·001
Current smoker (%)	25	26	0·7
Hypertension (%)	37	27	<0·05
Myocardial infarction (%)	12	11	0·6
Intermittent claudication (%)	4·5	1·6	<0·05

*χ^2 or Student's *t* test

Table 2 Prevalence and prevalence ratio of abdominal aortic aneurysm in men with and without a history of inguinal hernia

	History of inguinal hernia repair	No history of inguinal hernia	Prevalence ratio
Age (years)			
≥ 55	12·2 (7·0–17·4)	3·7 (2·8–4·6)	3·3 (2·0–5·3)
55–64	6·8 (0·0–14·6)	2·0 (1·1–2·9)	3·4 (1·0–11·1)
65–75	13·8 (6·0–21·5)	4·6 (3·0–6·2)	3·0 (1·6–5·7)
> 75	15·6 (23–28·9)	8·2 (4·5–11·8)	1·9 (0·8–4·8)
Never smoked	5·8 (0·0–12·3)	3·0 (1·9–5·1)	1·9 (0·5–7·0)
Former smoker	11·1 (3·1–19·1)	3·4 (2·3–4·5)	3·3 (1·5–7·1)
Current smoker	21·1 (7·4–34·6)	5·0 (2·9–7·0)	4·2 (2·1–8·2)

Values in parentheses are 95 per cent confidence intervals

The prevalence was highest in men with a history of inguinal hernia who currently smoked cigarettes: 21·1 (95 per cent c.i. 7·4–34·6) per cent. The prevalence ratio varied according to smoking status: 1·9 (95 per cent c.i. 0·5–7·0) per cent in never smokers, 3·3 (95 per cent c.i. 1·5–7·1) per cent in former smokers and 4·2 (95 per cent c.i. 2·1–8·2) per cent in current smokers.

For aneurysms larger than 50 mm (usually considered an indication for surgery), the prevalence in those with and without a history of inguinal hernia was 4·5 (95 per cent c.i. 1·2–7·8) per cent and 0·7 (95 per cent c.i. 0·2–1·1) per cent respectively; the prevalence ratio was 6·6 (95 per cent c.i. 2·6–16·6).

Discussion

In a group of 156 men with a history of inguinal hernia repair the prevalence of AAA was 12·2 (95 per cent c.i. 7·0–17·4) per cent, more than three times that in a group of 1771 men without a history of inguinal hernia.

Lehnert and Wadouh[10] described the relationship between AAA and inguinal hernia. They demonstrated an increased prevalence of inguinal hernia among patients with an abdominal aneurysm compared with patients with aortic occlusive disease. The present study confirmed these conclusions and quantified the prevalence of AAA among men with an inguinal hernia.

The increased risk among patients with inguinal hernia cannot be attributed to older age or more unfavourable cardiovascular risk. Even after adjusting for differences in age and cardiovascular indicators by means of multiple logistic regression analysis, the relative risk of AAA in men with, compared with those without, a history of inguinal hernia was 2·6 (95 per cent c.i. 1·3–5·4).

The increased prevalence of AAA in men with an inguinal hernia could be explained by the increased activity of elastase and collagenase, which has been described in both diseases[11,16,17]. This may eventually lead to degradation of supportive tissue in the aortic wall and the rectus muscle. The role of these enzymes in the pathogenesis of AAA has been confirmed in several studies[16,17]. The relationship between inguinal hernia in men and abnormalities in collagen composition of the rectus sheath has also been demonstrated[11,17].

The strong association between aneurysm and inguinal hernia in current smokers may be explained by an increase in α_1-antitrypsin activity in smokers[12]. α_1-Antitrypsin has been reported to lead to degradation of supportive tissue in patients with pulmonary emphysema[12] and inguinal hernia[18]. In addition, smoking may increase elastase activity in the aortic wall, which may promote aneurysm formation.

Men aged 55 years or older with a history of inguinal hernia are at increased risk of having an abdominal aneurysm, notably if they are cigarette smokers. As part of a selective screening programme, ultrasonography of the abdominal aorta could be considered before operation for inguinal hernia.

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Original article

Outcome of biofeedback for faecal incontinence

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Background: Biofeedback has been reported to improve or eliminate symptoms in approximately 70 per cent of patients with faecal incontinence. However, it is unknown which patients respond in relation to the different symptomatic types of faecal incontinence and the different structural sphincter aetiologies.

Methods: One hundred consecutive patients (84 women; median age 49 years) who completed biofeedback treatment were prospectively characterized by symptoms and by structural integrity of the internal and external anal sphincters as assessed endosonographically (87 patients). Patients underwent a median of 4 biofeedback sessions.

Results: Overall, 43 of the 100 patients regarded themselves as symptomatically cured and 24 improved after treatment. Cure or improvement was experienced by 24 of 30 patients with a structurally normal anal sphincter, by 27 of 46 patients with an external anal sphincter structural defect, and by seven of 11 with an isolated internal anal sphincter defect or atrophy. Thirty-three of 60 patients with urge incontinence alone were symptomatically cured, compared with five of 22 of those with only passive incontinence.

Conclusion: Biofeedback retraining is effective in the short term in treating a majority of patients with faecal incontinence. It is most successful in treating urge incontinence, but also helps some patients with passive leakage. Even in patients with structural anal sphincter damage, some symptom improvement or cure is achieved.

Paper accepted 17 May 1999

British Journal of Surgery 1999, 86, 1159–1163

Introduction

Faecal incontinence can arise as a result of anorectal dysfunction, or can occur in the presence of a normal anal sphincter mechanism if the stool is liquid or the bowel contracts vigorously[1]. Recent advances in investigative techniques, especially endoanal ultrasonography, enable accurate characterization of any underlying sphincter pathology[2]. External anal sphincter damage can often be repaired surgically. This helps a majority of patients in the short term[3,4], but some patients remain symptomatic despite an apparently good anatomical result. In others, surgery is not appropriate, is unlikely to achieve a good result, or would require a very invasive procedure such as a gracilis neosphincter or artificial sphincter. This includes patients with extensive damage, either of the external or internal[5] anal sphincters, weakness but no apparent structural damage, degenerative myopathy[6], and those with a normal sphincter but urgency[1]. Antidiarrhoeal drugs do not control symptoms in all patients. Even in those in whom there is a repairable lesion, it is unknown whether the residual functional capacity before repair would allow symptomatic improvement using behavioural techniques. Apart from surgical and drug treatment, few other options have been explored systematically.

Faecal incontinence has been the most commonly reported clinical use of biofeedback techniques. Enck[7], in a summary of published studies, concluded that there was an overall cure and improvement rate of 80 per cent. The major difficulty in interpreting these studies relates to the poor categorization of the treated patients. Nearly all studies predate the introduction of anal endosonography, so that the sphincter pathology in the treated patients was unknown.

This study reports the results in a prospective consecutive cohort of patients referred for biofeedback treatment of faecal incontinence. The patients were investigated before treatment, and the outcomes assessed in relation to the different types of pathology and symptomatology present. In particular, the authors wished to determine whether the presence of structural damage to one or both of the main sphincter muscles involved with continence, or atrophy involving the internal anal sphincter, would relate to the outcome.

Patients and methods

Patients were referred for biofeedback treatment of faecal incontinence by hospital consultants; as referral was by more than one consultant, there were no uniform criteria. Of 239 referred patients over a 2-year period, 26 patients (11 per cent) failed to commence, 11 (5 per cent) were assessed as inappropriate and 15 (6 per cent) failed to complete a course of treatment, often due to lack of motivation. Eighty-seven patients are still undergoing therapy. The results in the 100 patients who have completed treatment and been discharged are therefore reported.

These 100 patients were aged 14–82 (median 49) years. There were 84 women and 16 men. Sixteen had undergone previous surgery for faecal incontinence (12 anterior overlap sphincter repair, four postanal repair).

The main presenting complaint was urgency or urge incontinence (defined as an inability to defer defaecation and the urgent need to reach the toilet, or the loss of stool in the presence of urgency) in 60 patients, passive soiling (loss of stool not accompanied by an urge) or postdefaecation incontinence in 22, both passive and urge incontinence in 17, and incontinence for flatus only in one patient. However, patients often experienced overlap of symptoms. In addition, 31 patients also experienced some difficulty with evacuation of the bowels, although incontinence was the main complaint.

There was no apparent cause for the incontinence in 27 patients. In the remainder a variety of aetiologies was present, including obstetric sphincter damage and previous anal surgery. The duration of incontinence was from less than 1 year to over 30 years.

Eighty-seven patients had anal endosonography[8], performed by a consultant radiologist experienced in the technique. In 30 patients (34 per cent) both sphincters were structurally intact and of normal appearance, 19 (22 per cent) had an abnormal external anal sphincter, 11 (13 per cent) had an abnormal internal sphincter (defect or atrophy[6]) and in 27 (31 per cent) both sphincter muscles were abnormal.

Before treatment patients completed a 1-week bowel diary and symptom questionnaire. Treatment by the nurse specialist in continence (C.N.) usually involved four to six 1-h sessions.

Biofeedback treatment

Patients were treated lying in the lateral position. An air-filled manometric anal probe attached to a colour monitor (PRS 9300; Neen Healthcare, Dereham, UK) was used to assess the amplitude and duration of voluntary anal sphincter contraction, to show the patient how the sphincter was functioning, and to teach the patient to isolate anal sphincter contraction from buttock and abdominal effort. In the small proportion of patients who could not distinguish anal sphincter from abdominal wall contraction, surface electromyographic electrodes were used on the abdominal muscles at the same time.

Patients were taught: (1) maximal voluntary contraction ('squeeze as hard as you can, for as long as you can') concentrating on both the amplitude and duration of the contraction, with an effort to prevent the pressure from falling; (2) submaximal contraction ('squeeze halfway and see how long you can hold that for') – only for patients with an adequate maximal contraction, to build up the endurance of the contraction; and (3) fast-twitch contractions ('squeeze and relax as hard and fast as you can and see how many you can repeat before the muscle feels tired'). Each of these components was attempted several times in each session.

The patient was then given a programme of sphincter exercises to practise at home. Patients were allowed to continue taking loperamide or other constipating medication if previously prescribed, but all had not had adequate symptomatic benefit from this before referral. They were allowed to vary the dose of loperamide during treatment.

In addition, patients who were excessively sensitive on rectal distension testing, such as those with irritable bowel syndrome and urgency, or patients who were insensitive to distension, were also given feedback tuition with balloon distension. For those with an insensitive rectum the aim was to lower the threshold of first sensation, using progressively reduced volumes of balloon distension in the rectum, and for those with an excessively sensitive rectum the aim was to encourage relaxation and suppression of a feeling of urgency in response to increasing volume rectal balloon distension. Both disorders also involved instructing patients to coordinate the rectal distension with immediate and strong voluntary sphincter contraction.

Patients were usually seen at 2–4-week intervals and discharged when asymptomatic, satisfied with their outcome, or when there had been no progress in symptoms for two or more sessions and further progress seemed unlikely.

The home exercises recommended were similar to regimens of pelvic floor exercise often recommended by physiotherapists for urinary incontinence, but focusing on the anal sphincter rather than a vaginal contraction. Visual feedback was provided to show how the muscles work, and to help improve this.

Results

Patients had between two and eight (median 4) treatment sessions over 2–20 (median 5) months. At the final session

Table 1 Response to biofeedback by presenting complaint in 100 patients according to self-report at the final session

	Cured	Improved	No change
Urgency and urge incontinence ($n=60$)	33	13	14
Passive incontinence ($n=22$)	5	8	9
Both urge and passive incontinence ($n=17$)	5	3	9
Flatus incontinence only ($n=1$)	0	0	1
Total	43	24	33

Table 2 Relationship of anal ultrasonographic findings to clinical outcome in 87 patients

	Cured	Improved	No change
Both sphincters intact ($n=30$)	17	7	6
Abnormal EAS ($n=19$)	9	6	4
Abnormal IAS ($n=11$)	6	1	4
Both sphincters abnormal ($n=27$)	5	15	7

EAS, external anal sphincter; IAS, internal anal sphincter

symptoms were reported as 'cured' in 43 of the 100 patients, as 'improved' in 24 and as unchanged in 33. Men were more likely to report cure (ten of 16) than women, but the numbers were small.

Table 1 shows the relationship of the presenting main complaint to outcome. Patients whose main problem was urgency of defaecation were most likely to consider themselves cured. Those whose main complaint was passive soiling alone, or passive soiling combined with urgency, were least helped. However, this was not absolute: some patients with these symptoms achieved a cure or improvement.

Table 2 shows the relationship between endosonographic findings and outcome. Patients with normal structure and morphology of both sphincter muscles were most likely to be subjectively helped: 17 of 30 such patients considered the problem 'cured', whereas six were unchanged. Patients with defects in both sphincters were least likely to be helped, with seven of 27 'cured' and 15 reporting no change in symptoms.

Discussion

This study has demonstrated that, of an unselected consecutive group of patients, two-thirds were subjectively cured or improved by behavioural techniques. Although patients with structurally intact sphincters were the most likely to benefit, some with structural damage also benefited. This suggests that this treatment may be worth considering in patients with a range of underlying abnormalities, especially if surgery is not appropriate or the patient wishes to try a conservative treatment. To the authors' knowledge no previous study has assessed the value of this treatment in relation to the different underlying sphincter pathologies.

These results also reinforce the concept that the maintenance of continence is a complex process which depends not only on sphincter integrity, but also on the intimate relationship between stool consistency, large bowel and rectal function, residual sphincter function and psychological state. The improvement in patients with intact sphincters appears to relate to the ability of this treatment to modify the urgency. This may be mediated via a cerebral effect on large bowel function, via autonomic pathways and changes in stress levels with supportive treatment. Alternatively, enhanced ability to contract the anal sphincter is likely to diminish large bowel peristalsis and may even induce retrograde peristalsis[1,9,10], or may simply allow continence to be preserved until the urge (bowel contraction) ceases.

In patients with external sphincter damage, the treatment may lead to enhanced use of the residual functional capacity. Despite the appearance of external sphincter disruption, and an initially weak sphincter, some patients were able to develop a reasonable squeeze pressure and adequate sphincter function. A disruption of the external sphincter on endosonography should be regarded as a spectrum of abnormality. The anatomical derangement does not always correlate precisely with initial function or the potential function with retraining. Changes induced in large bowel function with the treatment may also tip the balance towards better continence. The response to treatment in some patients with internal sphincter weakness and degeneration, associated with passive soiling, is perhaps the most difficult to understand.

The treatment provided is a complex package of care. It involves retraining in relation to sphincter striated muscle function, but probably also modifies other autonomic function. In patients with constipation, biofeedback has been shown to modify central autonomic control of large bowel function, as measured using laser Doppler rectal mucosal blood flow[11]. Patients receive support and attention, and are taught about normal bowel function and about the symptoms and their cause. They are also given a disciplinary framework about toileting.

This study has also shown that some patients never manage to start or complete this treatment. Many lack the motivation or are unconvinced about the possible value of what they perceive to be 'simple exercises'. The treatment will be suitable only for patients who can follow a course of treatment, as the results are largely patient dependent, unlike drug or surgical therapy.

This study did not include a precise evaluation about the changes that occur in response to treatment with respect to anal manometry and rectal sensitivity. Many patients did improve the magnitude of, and ability to sustain, external sphincter contraction. Rectal sensory function also appeared to improve with treatment in some patients. These changes often correlated with symptomatic improvement. However, previous studies have shown a poor correlation between symptom improvement and changes in anal manometry[12], with more evidence suggesting a relationship between symptom improvement and change in rectal sensitivity. Further work on these aspects is required. Both anal sphincter pressure changes and changes in sensitivity are likely to be just a part of the complex response to treatment.

Many different techniques have been used in the name of 'biofeedback' to treat faecal incontinence. There is consensus amongst many studies that lowering the threshold for discrimination of rectal sensation of distension and synchronizing voluntary external anal sphincter contraction with reflex internal anal sphincter relaxation are both important factors in determining the success of biofeedback. The role of abolishing the delay between experiencing an urge to defaecate and contracting the anal sphincter, and of sphincter strengthening exercises, is less clear[12].

Some studies have used sphincter exercises to improve strength[13], duration[14], speed of recruitment of the external sphincter, and the ability to contract this muscle in isolation. Others have studied asymmetry of contraction and linked improvement to development of greater symmetry[15]. There is disagreement as to whether any of these parameters can be improved, and regarding their relationship to symptom improvement. Uncontrolled studies have suggested marked improvement in sphincter function and symptoms[16], whereas other more rigorous studies have found improvement unrelated to pressures[12]. Whitehead *et al.*[17] found biofeedback-assisted exercises more effective than anal sphincter exercises alone. All studies agree on the crucial role of patient motivation and the patient–therapist interaction. Enck[7] concluded that 'the mode of action is obscure'. Loening-Baucke[18] cast doubt on the efficacy of the biofeedback itself, concluding that the major effect was the 'placebo' effect of time, attention and general advice. The present authors do not regard these factors as placebo effects, but as important elements in a package of care.

There is a need to develop conservative options to increase patient choice and make therapy available to a wider range of patients. Biofeedback aims to increase patients' understanding of their condition and to enhance the individual's sense of control, which clinical observation suggests is often severely impaired amongst those with faecal incontinence. It also could potentially be made available in a wide variety of settings and may prove cost-efficient, which is important when managing such a common problem. It has no known adverse effects.

Subjective improvement was the outcome measure in this study. Future studies will demand more sophisticated outcome measures, and disease-specific quality-of-life tools are currently being developed for this purpose. The authors are also aware that the beneficial effects may not persist and that long-term evaluation is required.

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Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: role of total anatomical dissection

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Background: The wide variability of reported local recurrence rates after curative resection of rectal cancer without adjuvant therapy may be a consequence of many different factors. However, few studies have investigated the potential effects of such factors on local recurrence by multivariate analysis. The present study examined clinical and tumour characteristics, operation type and operative technique as potential predictors of local recurrence in patients treated by surgery alone.

Methods: Prospective data were analysed by bivariate and multivariate methods including actuarial survival and proportional hazards regression.

Results: Local recurrence (pelvic or pelvic and systemic) was diagnosed in 59 of 596 patients. The 5-year actuarial local recurrence rate was 11·1 (95 per cent confidence interval 8·7–14·3) per cent. Independent predictive factors for local recurrence were: positive nodes (hazard ratio (HR) 5·5, $P < 0.01$); distal margin of 1 cm or less (HR 3·8, $P < 0.01$); venous invasion (HR 2·0, $P = 0.02$) and total anatomical dissection of the rectum (HR 2·0, $P = 0.01$). There was no difference in local recurrence between patients who had the mesorectum divided and those in whom it was totally excised.

Conclusion: Nodal involvement is the most potent predictor of local recurrence. In patients in whom total anatomical dissection is performed, total mesorectal excision confers no additional protection against local recurrence.

Paper accepted 18 May 1999

British Journal of Surgery 1999, 86, 1164–1170

Introduction

The rates of local recurrence after resection of rectal cancer without adjuvant therapy reported in the English literature have varied widely over the past two decades[1]. Differences between rates may be due to case mix[2,3], surgical expertise[3–5], differences in definition of local recurrence (pelvic only *versus* pelvic recurrence in the presence of metastatic disease)[6–8], incomplete reporting of histopathological findings[9], lack of clarity in the definition of a curative operation[10], variability in the protocol for and length of follow-up[6,11], variability in data collection[12] and variability in the way in which local recurrence rates are calculated[8,13]. Furthermore, there have been few convincing studies of patient and tumour characteristics that might reliably predict local recurrence[14,15]. Such a study would require a large prospective patient cohort treated by standardized surgery alone, followed over a period of time sufficiently long for most local recurrences to occur, and would include a comprehensive range of clinical variables with standardized pathology and staging. Additionally, an independent audit of results would be desirable to ensure lack of bias.

The aim of this study was to identify the frequency of local recurrence in a patient population, to confirm this by independent audit, and to examine clinical and tumour characteristics, operation type and operative technique as potential predictors of local recurrence in patients treated by surgical resection alone.

Patients and methods

Since 1971, clinical, operative, pathology, adjuvant therapy and follow-up data on consecutive patients who had a resection for colorectal cancer were recorded prospectively in a computer database[16]. From 1979 the clinical and operative data were recorded by one surgeon (P.H.C.). Since the establishment of the database 90 per cent of all surgical specimens have been dissected and reported on by a single pathologist (R.C.N.), who also reviewed the histology of the remaining cases and coded the pathology data. Only patients with adenocarcinoma of the rectum (including the rectosigmoid junction but excluding the anal canal) were included in the analysis. Tumour site was measured from the anal verge using a rigid sigmoidoscope.

Surgical technique

A standard surgical technique was adopted in 1979[17]. In addition, total anatomical dissection was introduced in 1981 and has been performed by all members of the department since 1984. In this technique the rectum, surrounded by its fascial layers, was dissected by diathermy in the bloodless plane anterior and medial to the hypogastric plexus and its branches. In all patients undergoing a restorative procedure the splenic flexure was mobilized. The inferior mesenteric vein was ligated separately and divided at the lower border of the pancreas whenever necessary to ensure a tension-free anastomosis. The rectum was often, but not routinely, irrigated with water before anastomosis.

Total mesenteric excision *versus* non-total mesorectal excision

After total anatomical dissection a total mesorectal excision was performed only in patients with middle and lower third tumours. In these patients the rectum was divided so that the mesentery enveloped in its fascia was excised undisturbed. These patients were considered to have had a low anterior resection, an extended low anterior resection or an abdominoperineal excision depending on whether a restorative operation was performed. However, in upper third tumours, after total anatomical dissection, the mesorectum was divided and ligated rather than performing a total mesorectal excision. These patients were considered to have had a high anterior resection. In patients having a restorative operation a distal clearance of 2 cm was aimed for and confirmed by measurement in the unfixed specimen.

Examination of surgical specimen and tumour staging

All surgical specimens were examined according to a standard protocol[16]. The distal margin of clearance of the tumour was measured by the pathologist in the fresh unfixed specimen. The pathological definition of the circumferential line of resection applied since 1971[18] is equivalent to that subsequently described by Chan *et al.*[19] and by Quirk and co-workers[20].

All tumours were staged prospectively according to a clinicopathological system that has been validated by survival analysis[16]. This system permits the identification of patients with residual tumour in a line of resection only (including circumferential margin involvement), those with distant metastases only, and those with both. Such patients are classified as having a stage 'D' lesion[18]. These patients and those with a perforated tumour were considered, for the purposes of this study, to have had a palliative operation and were excluded from analysis. Patients with tumours classified as stage A, B or C without perforation were considered to have had a potentially curative operation.

Definition of local recurrence

Local recurrence was defined as clinically or radiologically suspected or biopsy confirmed tumour in the pelvis or perineal scar occurring with or without newly diagnosed distant metastases.

Patient follow-up and diagnosis of recurrence

This study was restricted to patients who were operated on between 1 January 1971 and 31 December 1991, and who were followed until death or at least to 31 December 1996. That is, all patients who had not died within 5 years of resection were followed for a minimum of 5 years.

Before 1993 all patients were reviewed in the outpatient department approximately every 3 months in the first year after resection, every 6 months in the second year and annually thereafter. Since 1993 patients have been reviewed every 3 months in the first year, then 6-monthly thereafter. The protocol comprised a physical examination, digital rectal examination and chest radiography. Colonoscopy and a variety of abdominal imaging techniques were performed at least annually on all patients. In addition, in patients with a suspected local recurrence, endoanal ultrasonography was often performed. Whenever possible biopsy confirmation was obtained.

To ensure accuracy of reporting, an independent and detailed audit of all patient hospital files and surgeons' case notes was conducted in 1996–1997 by a visiting surgeon (B.O.), who identified all patients who had developed a local recurrence. In addition a surgeon in this department (P.H.C.) reviewed the files and death certificates and interviewed the practitioners involved in follow-up of all patients who had died from causes other than colorectal cancer to ensure that there was no clinical evidence of local recurrence within 6 months before death.

Statistical methods

The χ^2 test was used to examine the statistical significance of differences in contingency tables. Time to local recurrence was measured from the date of resection until the date of confirmation of recurrence. In patients without local recurrence the censoring date was the date of death for those who died or the date when last known to be alive. Comparisons of time to recurrence between strata of categorical variables were made with the Kaplan–Meier method and the log rank test as implemented in the Statistical Package for the Social Sciences[21], which was also the source of the proportional hazards regression procedure. The assumption of proportional hazards was checked by examination of log(-log) plots[22]. The level for statistical significance was set at $P < 0.05$ and confidence intervals are at the 95 per cent level.

Results

A total of 832 resections were performed for rectal cancer between January 1971 and December 1991. Two hundred and thirty-six patients were excluded, 163 who had a palliative resection and 73 for the following reasons: carcinoma *in situ*, ulcerative colitis, Crohn's disease, metachronous tumour, death before discharge from hospital, adjuvant therapy, lost to follow-up before 5 years had elapsed, and no information regarding recurrence. Of the remaining 596 patients, 72 per cent were men and 28 per cent women. The mean(s.d.) age was 67(10) years. The level and size of tumour and the type of operation performed are summarized in *Table 1*. The overall prevalence of stages A, B and C tumours was 22·3, 37·8 and 39·9 per cent respectively, with no significant change over time.

Table 1 Features of the operation and the tumour in 596 patients

	No. of patients
Level (cm)	
≤7	188 (31·5)
7·1–11	178 (29·9)
>11	230 (38·6)
Size (cm)	
≤3 cm	128 (21·5)
3·1–6·9	380 (63·8)
≥7	88 (14·8)
Operation	
Abdominoperineal excision	174 (29·2)
High anterior resection	212 (35·6)
Low and extended low anterior resection and coloanal anastomosis	197 (33·1)
Hartmann procedure	13 (2·2)

Values in parentheses are percentages

By December 1996, 407 patients had died, 21 had been lost to follow-up and 168 were alive. Overall, the length of follow-up from resection to death from any cause or censoring ranged from 0 to 276 (median 67) months.

Local recurrence occurred in 59 patients, 41 of whom had a pelvic recurrence only and 18 had a pelvic and systemic recurrence. A further 111 patients had a systemic recurrence only and 426 had no recurrence.

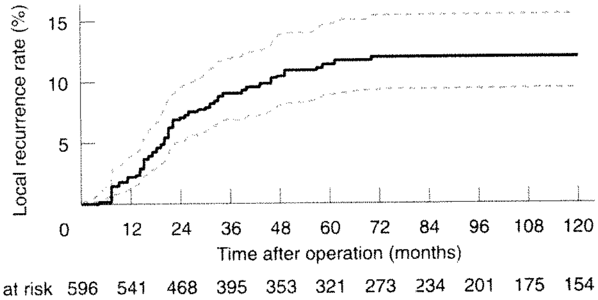

Fig. 1 Actuarial local recurrence rate with 95 per cent confidence intervals in 596 patients who underwent curative resection of rectal cancer

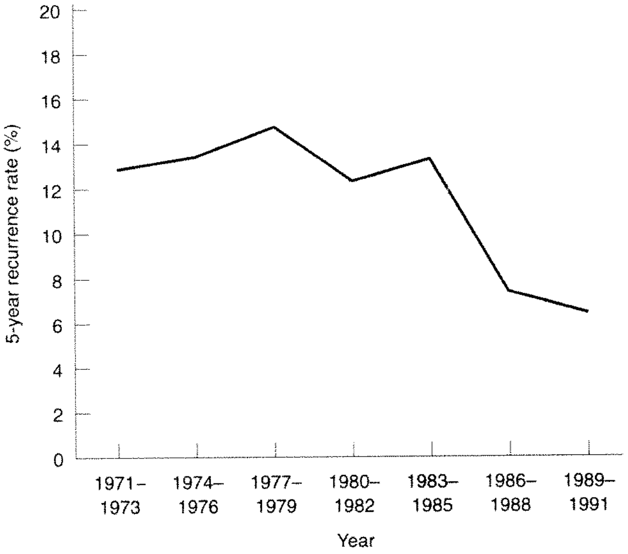

Fig. 2 Time trend in actuarial local recurrence rate in 596 patients who had curative excision of rectal cancer

Local recurrence: pelvic alone or pelvic plus systemic

In the 59 patients with local recurrence, time to recurrence ranged from 3·7 to 129·4 (median 20) months. Twenty-two per cent of local recurrences were diagnosed within 1 year, 64 per cent within 2 years, 80 per cent within 3 years, 90 per cent within 4 years and 95 per cent within 5 years. Actuarial local recurrence rates (with 95 per cent confidence intervals) were as follows: at 1 year 2·3 (1·3–3·9) per cent; at 2 years 7·0 (5·1–9·5) per cent; at 3 years 8·9 (6·7–11·7) per cent; at 4 years 10·3 (8·0–13·4) per cent; and at 5 years 11·1 (8·7–14·3) per cent (*Fig. 1*). *Fig. 2* shows that the local recurrence rate was a mean of 13 per cent from 1971 to 1985, then fell to a mean of 7 per cent for the remainder of the series ($P = 0{\cdot}03$).

Associations between local recurrence and other variables

There was no association between local recurrence and patient sex or age, level of the tumour, perioperative transfusion, tumour size or histological type. Five-year local recurrence rates were significantly raised where the distal margin of clearance was 1 cm or less, in tumours demonstrating high-grade or venous invasion, in ulcerating (but not polypoid or stenosing) tumours and in stage C tumours (*Table 2*). Although the local recurrence rate was lower in patients who had a total anatomical dissection than in those who did not, this difference was not significant.

Total *versus* non-total mesorectal excision

In patients who had a total anatomical dissection there was no difference in local recurrence rates between those who had the mesorectum ligated and divided (patients with upper third tumour having a high anterior resection) and those who had the mesorectum excised *in toto* (patients with middle or lower third tumours having a low or extended low anterior resection or an abdominoperineal excision) (5-year local recurrence rate 6·6 and 8·2 per cent respectively; $P = 0{\cdot}77$).

Table 2 Actuarial local recurrence rate by type of surgery and tumour pathology

	No. of patients	No. with recurrence	5-year recurrence rate (%)	P*
Operation†				
Restorative	409	42	11·5	0·94
Abdominoperineal excision	174	16	9·6	
Operation‡				
High anterior resection	212	16	8·2	0·06
Low and extended low anterior resection	197	26	15·2	
Procedure				
Total anatomical dissection	274	21	7·9	0·06
Non-total anatomical dissection	322	38	14·2	
Distal margin (cm)				
>2	472	47	11·0	0·92
≤2	124	12	11·5	
>1	557	50	9·9	0·01
≤1	39	9	27·2	
Macroscopic type				
Non-ulcerating	138	7	5·8	0·01
Ulcerating	458	52	12·9	
Grade				
Low or average	515	45	9·7	<0·01
High	81	14	23·3	
Venous invasion				
No	469	40	9·1	0·01
Yes	127	19	20·3	
Stage				
A	133	3	2·5	0·11
B	225	13	6·5	<0·01
C	238	43	22·6	

†Excluding 13 Hartmann procedures; excluding 13 Hartmann and 174 abdominoperineal excisions. *Log rank test

Multivariate analysis

All variables that had a significant or marginally significant bivariate association with local recurrence satisfied the proportional hazards assumption and were entered into a Cox regression model. Stage was dichotomized as stages A and B *versus* stage C. The model showed that ulceration and grade did not have independent effects on local recurrence. When these variables were excluded, the remaining variables were, in order of strength of their independent effects: stage C (hazard ratio (HR) 5·5, $P < 0 \cdot 01$), distal margin less than or equal to 1 cm (HR 3·8, $P < 0 \cdot 01$), venous invasion (HR 2·0, $P = 0 \cdot 02$), and not using a total anatomical dissection technique (HR 2·0, $P = 0 \cdot 01$).

Discussion

Several reviews have reported widely varying local recurrence rates[1,23,24] with significant clinical implications. Although surgical technique has been cited as an important variable[5] many other factors are often ignored. These have to be controlled before any conclusions can be drawn legitimately.

The precise definition of local recurrence is surprisingly lacking in many reports. There should be no confusion as to whether local recurrence refers to intrapelvic recurrence only or includes patients with newly diagnosed distant metastases in addition to intrapelvic recurrence, and whether patients with metachronous colorectal cancer have been excluded. Some studies define local recurrence as intrapelvic recurrence only, excluding patients who have intrapelvic recurrence and recurrence elsewhere, arguing that surgery can be responsible only for the 'local only' pattern of recurrence[15]. This ignores the possibility that distant metastases may have arisen from a pelvic recurrence and, in the alternative case, assumes that an exhaustive search failed to demonstrate the presence of synchronous distant metastases at the time of diagnosis of the local recurrence. In view of this, the definition of local recurrence in this study is that of pelvic recurrence with or without distant metastases.

Because local recurrence is related principally to tumour stage, series with different proportions of patients with stages A, B and C will have different rates. Therefore it is essential that studies report stage-specific local recurrence rates as well as an overall rate. For this reason, within a single study, accurate pathological examination using a comprehensive staging system is essential. All tumour margins should be examined thoroughly to exclude residual tumour in either the circumferential or longitudinal margins of resection. It is important for pathologist and surgeon to agree as to whether the operation was curative or palliative.

The deliberate or incidental selection of patients for inclusion in a study may bias recurrence rates. For example, the local recurrence rate in a tertiary referral hospital treating a relatively high proportion of patients with complex disease may be higher than that in a general hospital. Results may also be skewed in a series in which patients are carefully filtered for their suitability for a particular surgical approach[2].

Most reported series properly exclude patients who have had adjuvant therapy. However, this may lead to deflation of the local recurrence rate if adjuvant therapy was given more frequently in patients with stage C tumours, thus shifting the balance towards patients with a low risk of recurrence. This is especially relevant in series of patients operated on in the past decade[15].

Accurate ascertainment of recurrence depends on thorough prospective follow-up, preferably with independent validation of all data[13,25]. Reported studies frequently fail to describe the follow-up protocol in terms of how regularly patients were seen after operation and over what period, how many were lost to follow-up, what methods of surveillance were employed, and what steps were taken to verify that patients who died from causes other than colorectal cancer had not had a recurrence. Retrospective studies are flawed because of the likelihood of patients being lost to follow-up and consequent under-reporting of recurrence.

Recurrence is time dependent: the longer the follow-up time (up to about 5 years), the more recurrences will be detected. It is therefore essential that follow-up be conducted for a sufficiently long period to allow most recurrences to occur. Some studies report 1- or 2-year rates only[26,27], which will necessarily be lower than 5-year rates[28].

Most recent studies have used the actuarial method to calculate 5-year local recurrence rates, whereas earlier studies tended to report a crude rate where the numerator was the number of recurrences and the denominator was the number of operations performed. The actuarial method is clearly desirable as it takes account of the fact that recurrence is time dependent and also permits the inclusion of data from patients who have not been followed for a full 5 years. However, the actuarial method will yield a deflated 5-year rate if a substantial proportion of patients has not been followed for a full 5 years, for example when a study recruits patients over only 5 or 6 years and then analyses the results immediately. Related to this is the age distribution of patients. The older the patients, the more likely they are to die from causes other than colorectal cancer, reducing the number who might have had a recurrence if they had lived longer.

Once all the above factors have been controlled through careful definition and study design, there will still be uncontrolled variability from one series to another in factors that may influence the local recurrence rate, for example in stage distribution. These other factors then need to be controlled in statistical multivariate modelling in order to identify their independent contribution accurately.

This study has addressed all of these issues. In agreement with others, it was found that tumour stage was the most important predictor of local recurrence[15]. The only other pathological factor with an independent effect was venous invasion. After other factors were controlled, a distal margin of clearance of at least 1 cm and the adoption of a standardized technique of total anatomical dissection significantly reduced the incidence of local recurrence.

It has been suggested that total mesorectal excision is the best method of lowering the local recurrence rate[13,25]. The results of this study do not support this view as the rate was similar in patients who had total mesorectal excision and those in whom the mesorectum was transected. This finding suggests that dissection along anatomical planes rather than total excision of the mesentery is paramount. This is important because the recent literature has been very confusing, encouraging surgeons to perform a low anterior resection unnecessarily for tumours in the upper third of the rectum to achieve total mesorectal excision, thus putting the patient at increased risk of anastomotic leakage[29]. This point of view has now been recognized even by enthusiasts of total mesorectal excision[30].

Many reports have advocated the use of adjuvant therapies in patients with rectal cancer[31,32]. This study demonstrates that total anatomical dissection in unselected patients achieved a local recurrence rate of 8 per cent regardless of the type of operation. This rate compares more than favourably with those reported in randomized controlled trials of patients having adjuvant therapy[32]. In view of the considerable morbidity associated with adjuvant treatment[33], the present authors question its routine use without first ensuring optimal surgical technique.

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Experimental study of intraperitoneal suramin on the healing of colonic anastomoses

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Introduction: The effect of the antiangiogenic agent suramin on the healing of colonic anastomoses was studied in a rat model.

Methods: Rats underwent an end-to-end colonic anastomosis and its healing was tested by measuring bursting pressure, hydroxyproline content and number of newly formed vessels. For the bursting pressure experiment suramin was given intraperitoneally in a dose of 200 mg/kg (maximal tolerable dose) and 100 mg/kg. Hydroxyproline content and vessel density were only tested at 100 mg/kg since the toxicity at this dose was lower whereas bursting pressure was still diminished.

Results: There were no deaths. On the fourth day after operation bursting pressure in the control group was significantly higher than that in rats treated with suramin 200 mg/kg ($P = 0.006$) and 100 mg/kg ($P = 0.002$). Rupture occurred at the anastomotic line. On day 7, this difference was not statistically significant. Four days after the operation, the hydroxyproline content and vessel density were significantly below that in control segments (hydroxyproline: 10·3 *versus* 7·8 µg per mg dry weight; vessel content: 85·7 *versus* 49·6 vessels per × 100 field for control and suramin-treated rats respectively). On the seventh day no difference in hydroxyproline levels was seen but the vessel density was still diminished significantly ($P = 0.04$).

Conclusion: Experimentally, suramin significantly inhibits and delays healing of colonic anastomoses.

Presented in part to the XXXII Congress of the European Society for Surgical Research in Corfu, Greece, May 1997
Paper accepted 26 May 1999
British Journal of Surgery 1999, 86, 1171–1175

Introduction

In recent years it has become clear that angiogenesis plays a key role in the growth and metastatic pattern of various solid tumours. Microvessel density has been shown to be an independent prognostic factor in several carcinomas; in primary prostate[1], breast[2] and colorectal carcinomas[3] the presence of lymph node metastases correlates with the degree of angiogenesis. In addition, undetected micrometastases responsible for recurrent disease after so-called curative resections rely on new blood vessels to provide them with necessary nutritients.

From these observations interest has emerged in the use of antiangiogenic drugs in adjuvant treatment, for instance of colorectal carcinomas. The aim of using these agents is to keep the micrometastases in a small 'dormant state' rendering them more susceptible to the classical adjuvant therapies[4].

However, angiogenesis is necessary in the healing phase of a wound as is the case in a healing colorectal anastomosis. Therefore the use of antiangiogenic agents in the perioperative setting of colorectal resection of a malignancy might interfere with the normal healing of these anastomoses, causing important postoperative morbidity.

For these reasons, the effect of the antiangiogenic agent suramin on the healing of a left-sided colonic anastomosis was studied in a rat model. Healing was tested by measuring bursting pressure, hydroxyproline content was used as a measure of collagen synthesis and angiogenesis was monitored by quantification of vessel density.

Materials and methods

These studies were approved by the Institutional Animal Care and Use Committee, University Hospital of Antwerp.

Suramin (Germanin; Bayer, Leverkusen, Germany), a polysulphonated naphthylurea, was dissolved in 0·9 per cent sodium chloride and stored at a concentration of 25 mmol/l at −20°C until use.

All experiments were carried out double blind. While one investigator performed all colonic anastomoses, measurement of bursting pressures, hydroxyproline and vessel density was done by others.

Animals

A total of 112 male WAG/RIJ rats (Harlan CPB, Zeist, The Netherlands), weighing 150–250 g, were used in the study. Animals were housed individually in suspended mesh wire cages and fed a standard pellet diet (rat chow; Hope Farms, Woerden, The Netherlands) and water *ad libitum*. Animals were fasted for 12 h before surgical intervention. Housing was temperature controlled and provided a 12-h light–dark cycle.

Operative technique

Animals were anaesthetized using pentobarbital sodium injections (25 mg/kg intraperitoneally). Animals were fasted overnight to clean the colon and to minimize contamination of the peritoneal cavity and wound. The abdominal area was shaved and prepared using standard aseptic techniques. The skin was disinfected with a 10 per cent povidone–iodine solution. A 5-cm midline incision was made. The descending colon was identified and divided exactly 3 cm proximal from the rectal peritoneal reflection while preserving the vascular arcades. Anastomosis was performed using inverted and interrupted 5/0 coated silk sutures. The abdominal wall and the skin were closed separately using 4/0 polyglactin in a running fashion.

Analysis of anastomotic healing (*Table 1*)

Bursting pressure technique

Thirty-two rats underwent an end-to-end colonic anastomosis and were randomly allocated to two groups. Rats in group 1 served as controls ($n = 16$). Those in group 2 received the maximal tolerable dose (MTD) of suramin (200 mg/kg[5] intraperitoneally) the day of operation ($n = 16$). Within each group, half of the animals were killed on the fourth day after operation and half on the seventh day.

In a subsequent experiment, 20 rats underwent the same procedure and were divided into two groups: group 3 served as controls and group 4 received half the MTD of suramin, i.e. 100 mg/kg intraperitoneally. In this experiment animals were all killed on the fourth day because there was no diminution of bursting pressure on day 7 when suramin 200 mg/kg was used.

A 4-cm segment of colon including the anastomosis was dissected out *en bloc* in order to preserve the integrity of the anastomosis. One end of the separated colon was ligated. A blunt Shiley needle, secured into the other end, was then connected to the bursting pressure apparatus. This consisted of an infusion pump and a manometer. The pressure was recorded by an in-line pressure transducer and chart recorder. The isolated specimen was then submerged in a normal saline bath. The intraluminal pressure was increased at a constant rate of 0·5 ml air per min. Bursting pressure was determined by noting leakage of air or gross rupture of the anastomosis. Bursting pressure measurements were obtained within 5 min of death.

Quantification of hydroxyproline tissue content

Forty rats underwent an end-to-end colonic anastomosis and were randomly allocated to two groups: a control group, which received intraperitoneal saline, and a treated group which received intraperitoneal suramin 100 mg/kg. Within each group, ten rats were killed on both the fourth and seventh days after operation. A 1-cm segment with the anastomosis in the middle was collected for biochemical analysis. The samples were frozen in liquid nitrogen and sent for analysis to the University Hospital of Nijmegen. The segments were analysed for hydroxyproline as described by Hesp *et al.*[6]. Results were expressed as micrograms per gram of dry tissue.

Table 1 Study protocol

		Bursting pressure (mmHg)		Hydroxyproline (µg per mg dry tissue)	Vessel density (no. of vessels)
		200 mg/kg (n=32)	100 mg/kg (n=20)	100 mg/kg (n=40)	100 mg/kg (n=20)
Day 4	Control	64	85	10·3	85·7
	Suramin	35	51	7·8	49·6
Day 7	Control	128	–	17·8	90·2
	Suramin	125	–	18·7	71·1

Values are mean

Vessel density assessment

Twenty rats underwent an end-to-end colonic anastomosis and were randomly allocated to two groups: a control group, which received saline intraperitoneally, and a treated group which received intraperitoneal suramin 100 mg/kg. Within each group, five rats were killed at both 4 and 7 days after operation. Angiogenesis in tissue sections of this healing anastomosis was quantified according to a consensus report on this methodology[7]. In short, 1-cm segments of colon containing the anastomosis in the middle were immunostained for CD31 or platelet–endothelial cell adhesion molecule (Serotec, Oxford, UK). Diaminobenzidine was used as a chromogen. A light haematoxylin and eosin counterstaining was done. The three most vascular areas of the granulation tissue were selected at low-power magnification (× 100). In each of these vascular 'hot spots', individual microvessels were counted. Each brown-stained structure, independent of another, was regarded as a single vessel. The presence of a lumen or of red blood cells was not required. Co-staining inflammatory cells were excluded on morphological grounds. The mean value of the three counts per slide was used for further analysis. The high reproducibility of this method has been extensively documented[8].

Statistical analysis

All data are presented as mean(s.d.). Differences between groups in bursting pressure and hydroxyproline content were assessed with Student's t test. Mann–Whitney U test was used to compare the number of blood vessels in treated and untreated animals. Significance was defined as $P < 0{\cdot}05$.

Results

Body-weight and clinical survey

There were no deaths for the duration of the bursting pressure experiment. All rats lost weight after operation. Surgery alone induced a minimal reduction in body-weight, which amounted to approximately 7 per cent 1 day after operation. Preoperative weight was restored on the fourth day, whereafter normal growth was apparent. Suramin 200 mg/kg induced a far greater weight loss, maximal 3 days after injection and amounting to 15 per cent of preoperative weight. However, from this moment onwards normal growth was restored (group 2). Weight loss after suramin 100 mg/kg (group 4) was similar to that caused by surgery alone.

Macroscopic pathological assessment

At necropsy, all rats receiving suramin showed intra-abdominal bleeding, haemorrhaged testes and splenomegaly (spleen weights 0·52(0·10) g for controls *versus* 0·72(0·07) g after treatment with suramin 100 mg/kg; $P = 0{\cdot}0009$). No leaks or gross compromise of anastomotic sites or sequelae such as intra-abdominal abscess formation were noted. Ten suramin-treated animals showed accumulation of stool throughout the intestinal tract with the development of a subobstruction in two rats.

Analysis of anastomotic healing (*Table 1*)

Bursting pressure assessment

On the fourth day after operation, mean bursting pressure, a measure of resistance to increasing intraluminal pressure, after administration of suramin 200 mg/kg was significantly lower than that in the control group ($P = 0{\cdot}006$). The rupture occurred at the anastomotic line in both groups. On the seventh day, the bursting pressure had increased in both groups, but the difference between groups was not significant ($P = 0{\cdot}61$). In both control and suramin groups, on day 7 the rupture occurred outside the anastomosis. After reducing the suramin dose to 100 mg/kg, the differences in bursting pressure between the treated animals and controls on day 4 remained statistically significant ($P = 0{\cdot}002$). The differences in bursting pressure on the fourth day after operation between control groups (group 3: 85 mmHg; group 1: 64 mmHg) were not statistically significant as demonstrated by analysis of variance with the initial weights as co-variate (group 3: 206(4) g; group 1: 167(4) g; $P = 0{\cdot}16$).

Assessment of hydroxyproline content

Hydroxyproline, as a measure of collagen, was quantified in 5-mm segments containing the anastomosis in the middle. Four days after operation the hydroxyproline concentration within the anastomosis was significantly below that in the control segment ($P = 0{\cdot}001$). However, at 7 days, when concentrations in the control group had risen above those found in uninjured colon, anastomotic hydroxyproline concentrations showed no significant difference ($P = 0{\cdot}4$). The levels were 10·3(1·3) and 7·8(1·5) µg per mg dry weight on day 4, and 17·8(3·0) and 18·7(1·8) µg per mg on day 7 in control and suramin-treated animals respectively.

Vessel density assessment

Immunohistological measurements of vessel density made by counting the number of vessels within hot spots demonstrated a significant difference on day 4 ($P = 0{\cdot}004$) and on day 7 ($P = 0{\cdot}04$). The vessel density was 49·6(9·0) and 85·7(19·5) on day 4, and 71·1(28·4) and 90·2(19·6) on day 7 in suramin-treated and control animals respectively.

Discussion

This study demonstrates that systemic administration of an antiangiogenic agent impairs healing of left-sided colonic anastomotic sites. Suramin administration resulted in lower bursting pressures, and diminished stability of colonic anastomoses in the early healing phase within the first week. No differences could be demonstrated at 7 days, since bursting occurred at a site other than the anastomosis. Results of hydroxyproline and vessel density measurements also suggest that suramin unfavourably affects the rate of early anastomotic healing through mechanisms involved in collagen synthesis and angiogenesis. These results confirm the clinical data gathered retrospectively by Cole *et al.*[9] showing impaired wound healing in patients undergoing a major surgical procedure while receiving intravenous suramin; eighteen complications were encountered in five of a total of 14 patients. The predominant ones were haemorrhage requiring reintervention in five patients, impaired wound healing in three patients and bowel dysmotility in two.

As wound healing is a complex multistep process of overlapping phases including inflammation, formation of granulation tissue with angiogenesis and extracellular matrix remodelling, any factor disrupting one or more steps in this process will probably result in impaired wound healing. Initial coagulation is disturbed by suramin because of inhibition of clotting factors (V, VII, IV, X and XI), decreased clearance of endogenous heparin sulphate, increased circulating glycosaminoglycan anticoagulants and the potential to bind to the vascular endothelium with disruption of the coagulation cascade[10,11]. Many growth factors, which are messenger peptides secreted from a number of cell types integral to the repair mechanism, are inhibited in their activity by suramin. These include transforming growth factor β as a potent stimulator of the synthesis of matrix proteins, platelet-derived growth factor which is a major serum mitogen, basic fibroblast growth factor which has a major function as an angiogenesis peptide and epidermal growth factor which generally stimulates cell proliferation[12]. Only recently it was shown that suramin is also able to inhibit vascular endothelial growth factor[13]. Inhibition of one or more of these growth factors will finally end in disruption of their mitogenic and chemoattractant properties, inability to release cytokines, impaired promotion of angiogenesis and production of extracellular matrix. Suramin unbalances the ratio and nature of glycosaminoglycans within the extracellular matrix. This in turn negatively affects cross-linking of collagen fibrils and the migration of fibroblasts. Accumulation of glycosaminoglycan by inhibition of lysosomal enzymes required for its degradation can cause abnormal enlargement of various organs[14], including the spleen as was apparent in this study.

Several other adverse effects besides impaired wound healing have been demonstrated in this study. All suramin-treated animals had a weight loss that was more apparent than that in control rats. However, while this toxic effect may influence colonic healing, anastomotic healing is unaffected by a weight loss of the order suffered by the animals in the present study[15]. Bowel dysfunction may be explained by the ability of suramin to block growth factor–receptor interactions, direct cytotoxic effects through the disruption of membrane-based and intracellular enzyme systems, and induction of polyneuropathies with autonomic dysfunction[16,17].

In summary, this study has demonstrated that exogenous suramin significantly inhibits and delays healing of colonic anastomoses. The exact mechanism by which suramin mediates these effects is unknown but is almost certainly triggered by various factors. If these findings are confirmed with other antiangiogenic agents, the perioperative use of antiangiogenic agents in colorectal surgery for malignancy should be questioned.

Acknowledgements

The authors are grateful to Thijs Hendriks, Theo Wobbes and Ben de Man of the Department of Surgery, Academic Hospital of Nijmegen, for performing the biochemical analysis of hydroxyproline; to Frank Rylant for excellent histology work; and to Marleen Nysten for help in animal care and housing.

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Original article

Long-term functional results of colonic J pouch *versus* straight coloanal anastomosis

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Background: There are very few studies evaluating the long-term functional outcome of coloanal anastomoses. This retrospective study aimed to compare long-term functional results of straight and colonic J pouch anastomoses.

Methods: Thirty-seven patients, 25 with a straight anastomosis and 12 with a J pouch anastomosis, responded to a standardized telephone questionnaire. The mean time since surgery was 10 (range 4–18) years.

Results: The mean daily stool frequency was similar in both groups of patients (1·1 in patients with a reservoir, 1·5 in patients with a straight anastomosis). In both groups, two-thirds of patients had perfect continence or limited gas incontinence. Faecal incontinence was reported by two patients with a straight anastomosis and one patient with a pouch. Nocturnal stools and fragmentation were slightly more frequent in patients with a straight anastomosis. Half of the patients regularly used medication. Thirty-five of the 37 patients reported satisfaction with functional results.

Conclusion: Long-term functional results of coloanal anastomoses are satisfactory and, unlike early results, similar for both types of anastomosis. The functional benefit of a reservoir, seen in the first year after operation, is less evident with increasing time.

Paper accepted 26 May 1999

British Journal of Surgery 1999, 86, 1176–1179

Introduction

Since its description by Parks[1], low anterior resection with coloanal anastomosis has gained wide acceptance in the treatment of diseases of the rectum, especially cancer of the middle and lower thirds. Increasing acceptance of short distal margins[2–4] and a 5-year survival rate of about 70 per cent[5–7] have contributed to its increased use. Functional consequences of straight coloanal anastomosis, especially increased frequency and fragmentation of stools, have lead some authors to propose the incorporation of a colonic J pouch[8,9]. Several randomized prospective studies have compared the functional outcomes of both types of anastomosis 1 year after operation. All concluded that the colonic J pouch was superior[10–13]. Long-term functional results, however, have been studied less frequently[14–16].

In this institution, low anterior resection with coloanal anastomosis has been used since 1980. During the early years (1980–1987) only straight coloanal anastomoses were performed. Since 1987 a colonic reservoir has been incorporated in nearly half of the patients. The aim of this retrospective study was to compare the functional results of colonic J pouch and straight coloanal anastomosis at least 4 years after surgery.

Patients and methods

From June 1980 to February 1994, 77 patients underwent rectal excision with coloanal anastomosis. Up to February 1998, 30 of these patients had died, seven had been lost to follow-up and three had been reoperated on with resection of the anastomosis and formation of a definitive colostomy. The remaining 37 patients comprised the study population: 25 patients with a straight coloanal anastomosis (11 men and 14 women; mean age 57 (range 24–79) years) and 12 patients with a colonic J pouch anastomosis (four men and eight women; mean age 58 (range 44–67) years). The indications for surgery, anastomotic complications and early mean stool frequency, 1 year after the operation, are shown in *Table 1*.

Table 1 Indications for surgery, anastomotic complications and early stool frequency.

	Straight anastomosis ($n=25$)	J pouch ($n=12$)
Adenocarcinoma	21	9
Astler–Coller stage[17]		
A	4	1
B1	8	5
B2	3	1
C1	1	1
C2	5	1
Distance from anal margin (cm)*	6·8 (5·0–8·0)	6·9 (5·5–8·0)
Villous tumour	2	2
Rectal stenosis	0	1
Rectovaginal fistula	1	0
Solitary ulcer syndrome	1	0
Anastomotic leak	4	1
Anastomotic stricture	0	2
Early stool frequency (per day)*	2·9 (1–5)	1·3 (0·5–3)

*Values are mean (range)

Operative technique

The patient was positioned to allow a combined abdominal and perineal approach. The inferior mesenteric artery was ligated below the left colic artery. The descending colon and the splenic flexure were mobilized. The rectum was dissected down to the anorectal junction. The bowel was divided in the region of the mid-sigmoid colon. In 12 patients, a handsewn J-shaped colonic reservoir of 6–8 cm was constructed. From the perineal approach, a short mucosectomy was performed from just above the dentate line. All coloanal anastomoses were handsewn, using interrupted sutures of 3/0 polyglycolic acid. Each suture incorporated the full thickness of the colon. Straight coloanal anastomoses were either end to end (21 patients) or side to end (four patients). A temporary diverting stoma was constructed in 27 patients (right transverse colostomy in 14 patients, ileostomy in 13) and closed 3 months later. The choice of a straight or reservoir anastomosis was left to the operating surgeon's clinical judgement.

Functional assessment

Long-term functional results were assessed during the month of February 1998, using a standardized telephone questionnaire. To avoid bias, the investigator was not aware of the type of coloanal anastomosis that had been performed. Data obtained included daily stool frequency; experience of nocturnal stools; fragmentation; daytime and night-time continence; need to wear protecting pads; gas–stool discrimination; urgency; regular use of medication; need for a strict diet; restriction in social activities; and degree of satisfaction.

Table 2 Results

	Straight anastomosis ($n=25$)	J pouch ($n=12$)
Stool frequency (per day)*	1·5 (0·5–3)	1·1 (0·3–3)
Nocturnal stools	10	2
Stool fragmentation	10	3
Modified perception of the need to evacuate	11	5
Gas/stool discrimination		
Good	20	12
Doubtful	5	0
Urgency	7	3
Continence in daytime		
Perfect continence	6	2
Incontinence to gas	11	6
Minor leak	6	3
Faecal incontinence	2	1
Continence at night-time		
Perfect continence	17	9
Minor leak	7	3
Faecal incontinence	1	0
Wear of protecting pad	11	5
Regular use of medication		
Antidiarrhoeal	11	0
Laxative	2	7
Regular use of enemas	0	2
Restriction in certain food	14	6
Restriction in certain activities	5	3
Degree of satisfaction		
Fully satisfied or satisfied	23	12
Dissatisfied	2	0

*Values are mean (range)

Results

The mean time from operation to functional assessment was 10 (range 4–18) years in patients with a straight coloanal anastomosis and 8 (range 4–11) years in patients with a colonic J pouch anastomosis. Results are summarized in *Table 2*. The early mean daily stool frequency 1 year after the operation was 2·9 in the straight anastomosis group and 1·3 in the reservoir group. This had fallen to 1·5 and 1·1 per day respectively at the time of the study. Occasional nocturnal stools (ten of 25 patients *versus* two of 12) or fragmentation of stools (ten of 25 *versus* three of 12) were more frequently reported by patients with a straight anastomosis. Five patients in the straight anastomosis group reported difficulty in differentiating between gas and stools, compared with none in the reservoir group. The proportion of patients suffering from urgency or having a modified perception of the need to evacuate was similar in both groups.

Continence-related results were very similar in the two groups. Two-thirds of patients had perfect continence or troubles limited to gas incontinence, while one-quarter of patients reported minor leaks (occasional soiling with liquid stool). Incontinence to solid stools was reported by two patients with a straight anastomosis and one with a pouch. Episodes of faecal incontinence were frequent (more than twice a week) and occurred both in daytime and at night-time in one patient; they were rare (once a month or less) and occurred only in daytime in two patients. The proportion of patients wearing pads was similar in both groups.

The proportion of patients using medication to improve bowel function was nearly the same in both groups (straight anastomosis: 13 of 25 patients; J pouch: seven of 12), but the type of medication was different. The use of antidiarrhoeal medication was reported only by patients with a straight anastomosis. The use of laxative medication was more frequent in patients with a pouch. Two patients regularly used enemas to elicit evacuation of the pouch. In both groups, at least half of the patients avoided particular foods, and nearly one-quarter of patients avoided certain activities (mainly long journeys by car or aeroplane) because of faecal incontinence (one patient) or urgency (seven patients).

Thirty-five of the 37 patients were either 'fully satisfied' or 'satisfied' with functional results. Two patients in the straight anastomosis group reported dissatisfaction, compared with none in the reservoir group. The cause of dissatisfaction was faecal incontinence for one patient and delayed return to adequate function for the other.

Discussion

The present study is neither prospective nor randomized and the sample sizes are low. For this reason, statistical comparisons were not performed because they would have lacked power. However, the main interest of this purely descriptive study is the mean time between surgery and functional assessment, 10 years, which is the longest reported so far.

The easiest way to appreciate functional results is to consider the degree of patient satisfaction. In view of the high satisfaction rate observed, long-term results after low anterior resection with coloanal anastomosis seem excellent. However, this subjective criterion does not yield an accurate reflection of functional results, mainly because 27 of 37 patients had a temporary diverting stoma, which might have improved their acceptance of minor symptoms, and because 30 of the patients survived cancer and the relief of being cured certainly influenced their degree of satisfaction.

Regarding continence, early results of coloanal anastomoses are generally satisfying: incontinence to gas and minor leaks are frequent, but real faecal incontinence is rare and even absent in some series[8,18,19]. The present study suggests that these results do not change over time. Unlike some series[10,12], no difference was observed between patients with a straight anastomosis and those with a reservoir.

In the first year after operation, the mean stool frequency is known to be significantly lower in patients with a reservoir than in those with a straight anastomosis[10–13]. In the present study, the mean stool frequency was close in the two groups of patients (1·1 *versus* 1·5). For patients with a reservoir, it was consistent with published values[10,11,18–20], whereas for patients with a straight anastomosis it was very low compared with previous data[10,11,18,21]. A possible explanation is the long time elapsed since the operation. An improvement in function, with a decrease in stool frequency, during the first 2 years after operation is generally seen with both types of anastomosis[11,15]. The present study suggests that results for colonic J pouch anastomoses remain stable beyond these 2 years, while those for straight anastomoses continue to improve. However, the assessment of the stool frequency is biased, since a lot of patients used medication to improve bowel function. The medication required depended on the type of anastomosis: antidiarrhoeal medication in patients with a straight anastomosis, and laxatives and enemas in patients with a reservoir.

Some functional complaints may persist long after the operation. In the present study, as in that of Dehni *et al.*[16], fragmentation of stools was the most frequent complaint. Defined as multiple evacuations at short intervals, over a 1–2-h period, with persistence between evacuations of a sensation of 'rectal fullness', fragmentation has been reported to be less frequent when a colonic J pouch is fashioned[11]. This was observed in the present study. Unlike stool frequency, fragmentation does not seem to improve with time. Indeed, the fragmentation rates observed are close to those reported by Berger *et al.*[19] (colonic J pouch anastomosis) and Paty *et al.*[14] (straight coloanal anastomosis). Urgency also seems common long after the operation. In the present study it was the main cause of limitation of social activities and, unlike in some series, it was irrelevant to the type of anastomosis. Inability to differentiate between gas and stools may also persist long after the operation. In the present series, this was only experienced by patients with a straight anastomosis, but other authors have observed it in patients with a reservoir[18]. Occasional episodes of nocturnal stools seem less frequent in patients with a reservoir. The perception of the need to evacuate is frequently modified with both types of anastomosis.

The long-term functional results of coloanal anastomoses are satisfactory; the majority of patients have an almost normal life and, unlike early results, long-term outcome seems very similar with both types of anastomosis, especially with respect to daily stool frequency. Similar findings were recently reported by Joo *et al.*[15]. The present study suggests that the functional superiority of the colonic J pouch observed in the first year after operation does not persist in the long term. The real advantage of the colonic reservoir seems to be the rapidity with which good functional results are obtained.

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Impact of laparoscopic colonic resection on tumour growth and spread in an experimental model

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Background: The influence of surgical manipulation and carbon dioxide pneumoperitoneum on intraperitoneal tumour growth and port-site metastasis during laparoscopic colon resection is still unknown.

Methods: Some 33 male WAG/Rij rats were randomized into three experimental groups: a laparoscopy group with carbon dioxide pneumoperitoneum ($n = 11$), a gasless laparoscopy group ($n = 11$) and a laparotomy group ($n = 11$). After transanal injection of a tumour cell suspension (1×10^6 CC531 cells) into the distal colon, a colon segment resection and an end-to-end anastomosis (laparoscopy; intra-abdominal technique) were performed. Tumour growth was scored semiquantitatively 24 days after the operation. Data were analysed by the Kruskal–Wallis test.

Results: The tumour indices from the four locations with the greatest tumour growth were significantly decreased in the laparoscopy group with carbon dioxide pneumoperitoneum compared with the gasless laparoscopy and laparotomy groups ($P < 0{\cdot}01$). Port-site metastases were significantly decreased in the carbon dioxide pneumoperitoneum group compared with the gasless laparoscopy group ($P = 0{\cdot}05$).

Conclusion: A full laparotomy incision promotes greater tumour growth than does carbon dioxide pneumoperitoneum. Surgical manipulation stimulates local tumour spread more than the establishment of a carbon dioxide pneumoperitoneum.

Paper accepted 27 April 1999

British Journal of Surgery 1999, 86, 1180–1184

Introduction

The effects of laparoscopic surgery on tumour growth and spread remain unclear. Reports of implantation and intraperitoneal tumour dissemination after laparoscopic procedures in patients with intra-abdominal malignancy are a source of increasing concern and represent the most important factor that precludes widespread employment of laparoscopy in the treatment of malignant disease[1].

Recent experimental studies suggest a multifactorial aetiology for laparoscopic tumour spread. *In vitro* experiments have suggested a promoting effect of carbon dioxide on the growth of cancer cells[2]. However, tumour growth *in vivo* is always subject to the systemic immunological effects resulting from surgical intervention. Procedures effected in rats through small incisions resulted in preservation of postoperative systemic immune function[3]. In accordance with these findings, greater peritoneal tumour growth was found after laparotomy than after carbon dioxide pneumoperitoneum in a solid tumour model as well as in a cell suspension model in the rat; however, gasless laparoscopy was associated with fewer port-site metastases and less tumour growth than carbon dioxide laparoscopy[4]. A full laparotomy incision appears to have a greater effect than does carbon dioxide pneumoperitoneum on postoperative tumour growth, but insufflation of carbon dioxide has recognized local and systemic side-effects. One question, therefore, is whether gasless techniques are superior to carbon dioxide laparoscopy in cancer surgery. The pressure and insufflation time may influence the experimental results of tumour cell dissemination and malignant cell growth.

However, tumour spread after surgical procedures does not depend only on the route of access and exposure. Complex surgical techniques, procedure and manipulation time, local tissue trauma and general aspects of the operative technique must also be considered. In a realistic experimental set-up these factors should be comparable to the clinical situation.

The purpose of the present study was to include important factors in cancer surgery and to reconcile the effects of tumour recurrence that may be associated with minimally invasive surgery in a colorectal cancer model. The recently described model of laparoscopic colon surgery in the rat was modified to include local tumour cell spillage from the manipulation site during segment resection followed by creation of intraperitoneal anastomoses[5,6].

Materials and methods

Animals

Thirty-three male inbred WAG/Rij rats weighing 150–180 g were kept under standard laboratory conditions (12 h light/12 h dark, room temperature 25°C, relative humidity 55 per cent) with free access to standard laboratory diet and water *ad libitum*.

Tumour

CC 531 is a 1,2-dimethylhydrazine-induced, weakly immunogenic, moderately differentiated colon adenocarcinoma, transplantable in syngeneic WAG/Rij rats. The cells were cultured in RPMI 1640 medium, 2 per cent Hepes buffer solution, 1 per cent streptomycin–penicillin and 5 per cent fetal calf serum at 37°C in an atmosphere of 5 per cent carbon dioxide. Before use, the cells were washed with phosphate-buffered saline, trypsinized for 5 min and centrifuged for 5 min at 1200 r.p.m. Viable cells were counted using trypan blue exclusion. Viability always exceeded 95 per cent. To establish the tumour model, a concentration of 1×10^6 cells/ml was used.

Operative groups

The animals were randomized into three different operative groups: a conventional laparotomy group ($n = 11$), a laparoscopy group with carbon dioxide pneumoperitoneum ($n = 11$) and a gasless laparoscopy group ($n = 11$). All procedures were performed by one surgeon with wide experience of the different surgical techniques.

Operative procedures

The rats were anaesthetized by intraperitoneal injection of pentobarbital sodium 0·5 ml per 100 mg and fixed in the supine position.

Conventional laparotomy

For conventional laparotomy, the animals underwent a 6-cm midline incision. The viscera were separated and the colon was exteriorized. A probe 8 cm in length was inserted transanally into the colon and 1 ml of the tumour cell suspension was injected. A colon segment of 1 cm was resected and an end-to-end anastomosis was performed using a 7/0 suture. Total operating time was 90 min.

Laparoscopy with carbon dioxide pneumoperitoneum

A Veress needle was inserted between the middle and lower thirds of the space between the xiphoid and pubis, and a pneumoperitoneum of 7 mmHg was created using an electronic laparoflator (Aesculap, Tuttlingen, Germany). A laparoscopic sheath with an insufflation side port followed by a 4-mm arthroscope was inserted mid-abdominally. Under direct vision, two operating ports were implanted in the lower abdomen. The tumour cell suspension was injected transanally. Colon segment resection and end-to-end anastomosis were performed intracorporally using a 7/0 suture. Total operating time was 90 min.

Gasless laparoscopy

An abdominal wall lift was performed using two abdominal retraction wires. A laparoscopic sheath and 4-mm arthroscope were inserted and two operating ports were implanted. Colon resection and end-to-end anastomosis were performed intracorporally with a 7/0 suture. Total operating time was 90 min.

Evaluation

During the first 7 days after operation the rats were weighed daily, and once a week thereafter. Some 24 days following operation all animals were killed and intraperitoneal tumour growth was scored with a semiquantitative cancer index[7] (*Table 1*). The score was assessed by two independent observers. Tumour growth was evaluated in the subcutis (abdominal wall metastasis), parietal peritoneum, anastomosis, mesentery, liver, kidney, retroperitoneum, omentum and scrotal fat. Additionally, the cancer indices at the four sites with the greatest tumour growth and the four sites with

Table 1 Cancer index scoring

Cancer index	Diameter of tumour nodules
0	No tumour
1	Diameter less than 0·5 cm
2	Diameter between 0·5 and 1·0 cm
3	Diameter between 1·0 and 2·0 cm
4	Diameter between 2·0 and 3·0 cm
5	Diameter exceeding 3·0 cm

the least tumour growth were determined. The anastomosis was excised and weighed.

Statistical analysis

Mean and standard deviation were calculated. To analyse the data for significant differences between the groups, the Kruskal–Wallis test (global test) and the Dunn test with α correction were performed.

Results

One animal in the carbon dioxide pneumoperitoneum group and one in the laparotomy group died from anaesthesia. Thirty-one animals survived the operative procedure and could be evaluated 24 days following surgery. No unexpected morbidity or death occurred after colon surgery.

Manipulation time

The manipulation time varied from 7 to 17 (mean 12) min in the laparotomy group, from 20 to 37 (mean 26) min in the laparoscopy group with carbon dioxide pneumoperitoneum and from 28 to 55 (mean 40) min in the gasless laparoscopy group.

Body-weight

Body-weight decreased after operation in all groups during the first 7 days with a maximum of 5 per cent. In the following weeks the body-weight recovered up to 120 per cent of the preoperative value. In the last 4 days of the experiment, the weight almost reached a plateau. No significant differences between the three experimental groups were found.

Cancer index

Total tumour load

The cancer indices from the four locations with greatest tumour growth were significantly lower in the laparoscopy group with carbon dioxide pneumoperitoneum ($P < 0{\cdot}01$) than in the gasless laparoscopy group ($P = 0{\cdot}002$) and the laparotomy group ($P = 0{\cdot}01$). This was confirmed by the total value of the cancer indices from the four locations with the least tumour growth ($P = 0{\cdot}01$). No significant difference in total tumour load was found between the gasless laparoscopy group and the laparotomy group (*Fig. 1*).

Port sites

In the carbon dioxide pneumoperitoneum group, one animal developed tumour nodes in the subcutis of the abdominal incision sites, compared with seven in the gasless laparoscopy group and five in the laparotomy group. The cancer indices scored in the subcutis were significantly decreased in the pneumoperitoneum group compared with the gasless laparoscopy group ($P = 0{\cdot}05$).

Liver

Tumour growth in the liver was found in three animals in the carbon dioxide pneumoperitoneum group, and in all animals in the gasless laparoscopy and laparotomy groups. Cancer indices scored for the liver were significantly lower in the pneumoperitoneum group than the gasless laparoscopy group ($P = 0{\cdot}002$).

Kidney

Three animals in the carbon dioxide pneumoperitoneum group developed kidney metastases, compared with nine in each of the gasless laparoscopy and laparotomy groups. The cancer indices scored for the kidney were significantly lower in the pneumoperitoneum group than the gasless laparoscopy group ($P = 0{\cdot}009$).

Anastomosis

All animals in the three experimental groups developed tumour growth in the area of the anastomosis. The cancer index ranged from 1 to 4 (mean 2·0) in the carbon dioxide laparoscopy group, from 1 to 5 (mean 4·0) in the gasless laparoscopy group and from 2 to 5 (mean 4·1) in the

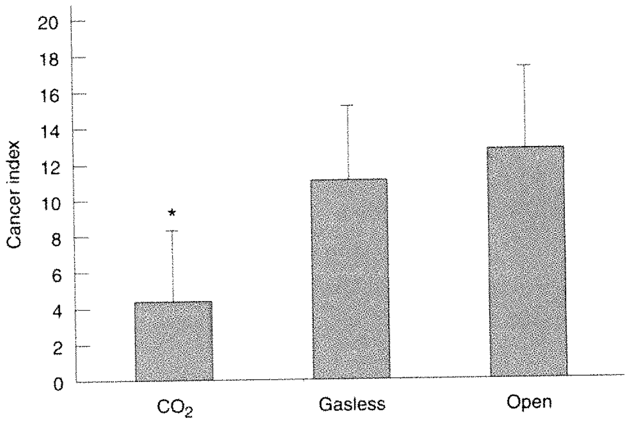

Fig. 1 Mean(s.d.) cancer index of the three operative groups at the four sites with the most tumour growth. $^{*}P < 0{\cdot}01$ (Kruskal–Wallis test)

Table 2 Tumour growth assessed as mean cancer index at different abdominal sites in the carbon dioxide pneumoperitoneum, gasless laparoscopy and open laparotomy groups

Abdominal site	Carbon dioxide ($n = 10$)	Gasless ($n = 11$)	Open ($n = 10$)	P*
Port site	0·1†	1·5	1·3	0·05
Kidney	0·5	1·4	2·1	0·009
Retroperitoneum	0·9	1·9	1·9	0·122
Liver	0·5†	1·6	1·1	0·002
Scrotal fat	0·9†	2·3	2·3	0·008
Omentum	1·0†	2·7	3·2	0·013
Mesentery	1·8†	4·1	4·1	0·0006
Anastomosis	2·0†	4·0	4·1	0·005
Total tumour load	0·1†	1·5	1·3	0·002

*Kruskal–Wallis test. †$P < 0\cdot 05$ *versus* gasless laparoscopy group and *versus* open laparotomy group (Dunn–Holm test); there were no significant differences between the gasless laparoscopy and open laparotomy groups

laparotomy group. At the anastomosis there were significant differences between the cancer indices of the pneumoperitoneum group and those of the gasless group ($P = 0\cdot 005$) and the laparotomy group ($P = 0\cdot 005$) (*Table 2*).

Weight of anastomosis

The weight of the anastomosis ranged from 0·3 to 11·5 (mean 4·7) g in the laparotomy group, from 0·1 to 3·7 (mean 0·9) g in the carbon dioxide pneumoperitoneum group and from 0·2 to 7·2 (mean 3·9) g in the gasless laparoscopy group. The anastomosis weighed significantly less in the carbon dioxide pneumoperitoneum than in the gasless laparoscopy and laparotomy groups ($P < 0\cdot 01$). There was no difference between the weight of the anastomosis in the gasless laparoscopy group and the open group ($P > 0\cdot 05$).

Discussion

Laparoscopic surgery for colorectal cancer has been suggested to result in an earlier return of bowel function, earlier discharge of the patient from the hospital, and a more rapid return to work and activities of daily living, but is suspected of being responsible for previously unrecognized patterns of tumour spread such as port-site recurrence and unexpected peritoneal carcinomatosis[1]. The overall incidence of these phenomena cannot be determined given that the total number of patients undergoing such procedures is unknown. Several aspects of laparoscopic surgery for treatment of malignant disease have been deemed to be responsible for an increased probability of wound implantation and peritoneal tumour growth. The increase in exfoliation of tumour cells may result from greater manipulation with laparoscopic instruments near the tumour or at the tumour itself. Instruments and port sites may be contaminated by malignant cells during manipulation and extraction of the specimen[8]. A direct physical and chemical influence of the pneumoperitoneum and pressure on tumour cell diffusion and malignant cell growth have been mentioned[2]. In view of recent experimental investigations and the complexity of the clinical situation, a multifactorial aetiology of tumour recurrence after laparoscopy must be considered.

The present study extends the technique of laparoscopic colon surgery in a recently described rat model[5] to include the gasless laparoscopic approach. The feasibility of laparoscopic colon resection in the rat while performing intra-abdominal sutured anastomosis has been already demonstrated. CC531 moderately differentiated colon adenocarcinoma cells injected into the peritoneal cavity of syngeneic WAG/Rij rats at the time of a surgical procedure have proved to be a good model for studying the spread of cancer[4]. Umpleby *et al.*[9] have shown that free viable cancer cells occur in the peritoneal cavity in 70 per cent of all patients with colorectal cancer. This observation provides a basis for justifying the cell suspension model, because free viable cells can implant at the peritoneum and the trocar sites. The direct implantation of tumour cells that occurs during manipulation in the operating field or when a specimen is removed through a narrow incision on the abdominal wall was only partly considered in the cell suspension model. However, a solid colon cancer model in the rat is not available. To include both direct and indirect implantation of tumour cells in the present study, the cell suspension model was modified, in order to introduce cancer cells into the lumen of the distal colon. Using this technique, the cell-containing segment of the colon represents the origin of tumour spillage during resection and anastomosis of the colon. This technique may simulate the clinical situation better than the cell suspension model. To include the adverse effects of a carbon dioxide pneumoperitoneum on physiological function, a sufficient procedure time of 90 min and an intra-abdominal pressure of 7 mmHg were selected for creation of a pneumoperitoneum. Recent experiments in the rat[10] have demonstrated that under these conditions portal venous blood flow is reduced by about 50 per cent. A comparable depression of blood flow in the human portal vein occurs with a pressure of 12–14 mmHg[11].

In contrast to previous studies, in the present study there was no difference in postoperative body-weight between the three groups, owing to the complex and realistic experimental set-up[12]. Port-site recurrence and intraperitoneal tumour growth were significantly lower in the laparoscopy group with carbon dioxide pneumoperitoneum than in the gasless laparoscopy and laparotomy groups. Abdominal surgery, performed via either a large incision or via the laparoscopic approach, may systemically encourage tumour growth in the postoperative period. A full laparotomy incision appears to have a significantly greater effect than a carbon dioxide pneumoperitoneum on postoperative immunosuppression and tumour growth. These findings accord with previous investigations. Allendorf *et al.*[13] compared a full laparotomy incision in mice with a carbon dioxide pneumoperitoneum. In the laparotomy group tumours were significantly larger than those in the pneumoperitoneum and control groups. Bouvy *et al.*[14] compared tumour growth after open and laparoscopically assisted small bowel resection in rats. The mean tumour size in the open group was significantly greater than that in the laparoscopically assisted group. In a further study with rats using colon cancer cell suspensions, Bouvy *et al.*[4] recorded greater tumour growth after laparotomy in comparison to carbon dioxide pneumoperitoneum and greater peritoneal tumour growth in the carbon dioxide group than in a gasless group. In this study the procedure lasted only 20 min, and a real operation was not carried out. Gasless laparoscopy avoids local and systemic side-effects of carbon dioxide insufflation.

The results of the present study contrast with the data of Bouvy *et al.* in that the gasless laparoscopy group had greater intraperitoneal tumour growth and more port-site metastases than the carbon dioxide pneumoperitoneum group. Even the tumour load of the anastomosis, corresponding to the weight of the anastomosis, was significantly greater without pneumoperitoneum. Gasless laparoscopic colon resection is technically difficult, because exposure of the distal colon by mechanical retraction is limited. Although the same operation was carried out in both groups, the manipulation time for colon segment resection in the gasless laparoscopy group was much longer than that in the pneumoperitoneum group. Generally, surgical manipulation increases tissue trauma, local inflammation, systemic postoperative immunosuppression and may promote malignant cell growth[15,16]. However, colon segment resection and suturing the anastomosis laparoscopically in the abdomen of the rat, as in the present study, are very demanding operative procedures causing much tissue trauma. The higher incidence of port-site metastases in the gasless group might be a result of greater tissue trauma and mechanical contamination of the port site with instruments owing to the long manipulation time. The results of the study do not suggest that laparoscopy with pneumoperitoneum is generally a better surgical procedure than gasless laparoscopy but in complex procedures this surgical technique appeared to have great influence on tumour spread.

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Original article

Desmoid tumours complicating familial adenomatous polyposis

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Background: Desmoid tumours are one of the most important and intriguing extracolonic manifestations of familial adenomatous polyposis (FAP). They have been studied only in small numbers of patients.

Methods: Patients with FAP who also had desmoid tumour were identified from a polyposis registry database and their hospital notes were reviewed.

Results: There were 166 desmoids in 88 patients (median age 32 (interquartile range 22–38) years; 51 (58 per cent) female); 83 tumours (50 per cent) were within the abdomen and 80 (48 per cent) were in the abdominal wall. All but 16 individuals (18 per cent) had already undergone abdominal surgery, which was significantly more recent in women ($P = 0.01$, Mann–Whitney U test). Intra-abdominal desmoids caused small bowel and ureteric obstruction and resulted in ten deaths; survival was significantly poorer than in patients with abdominal wall desmoid alone ($\chi^2 = 3.93$, 1 d.f., $P = 0.047$, log rank test), and eight of 22 patients who underwent resection of intra-abdominal desmoid died in the perioperative period.

Conclusion: Abdominal wall desmoids caused no deaths or significant morbidity; although recurrence was common after excision, the treatment was safe. Intra-abdominal desmoids can cause serious complications and treatment is often unsuccessful; in particular, surgery for desmoids at this site is hazardous.

Paper accepted 26 May 1999

British Journal of Surgery 1999, 86, 1185–1189

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant condition caused by germline mutation of the *APC* tumour suppressor gene, which occurs with a frequency of approximately one in 7500 of the population[1]; about 15 per cent of cases result from a new, rather than an inherited, mutation. The defining feature of FAP is the development of multiple adenomatous large bowel polyps in childhood and adolescence which inevitably progress to colorectal carcinoma[2], so that patients are usually treated by prophylactic colectomy in their teens or early twenties.

FAP is now recognized to be a more generalized disorder, in which a spectrum of extracolonic manifestations occurs[3]. Desmoid tumours – poorly understood, locally invasive proliferations of myofibroblasts which arise in about 10 per cent of patients with FAP[4] – are one of the most important of these as they contribute significantly to morbidity and mortality rates[5]. Their importance is likely to increase as improvements in screening and management of the large bowel and, more recently, upper gastrointestinal screening by endoscopy further reduce the number of deaths from rectal and upper gastrointestinal malignancy[6].

Trauma (particularly surgical), oestrogens and the presence of a particular range of *APC* mutations have been implicated in the aetiology of desmoids, although their natural history remains obscure. A variety of treatments, including surgical excision, non-steroidal anti-inflammatory drugs (NSAIDs), antioestrogens and cytotoxic chemotherapy have been advocated, but good evidence for the efficacy of most of these is lacking[4], because only small numbers of patients with FAP and associated desmoids have been studied.

Patients and methods

All patients with FAP registered with the St Mark's Hospital Polyposis Registry who also had desmoid disease were identified by a search of the Polyposis Registry database. The Registry records, hospital notes and pathology reports of these patients were examined.

Particular note was made of the anatomical site of the desmoids, the age at which they were diagnosed, their relationship to previous surgery and any history of desmoid tumour in a first-degree relative. In women, obstetric history and combined oral contraceptive and hormone replacement therapy use was recorded. In each case treatment given and outcome were detailed.

Statistical analysis

Differences in proportions were tested with the χ^2 test (with Yates correction), and medians were compared with the Mann–Whitney *U* test. Survival estimates were calculated by the Kaplan–Meier method and compared by means of the log rank test. $P < 0·05$ was considered to be statistically significant.

Results

Presentation and complications

A total of 166 distinct desmoid tumours were documented in 88 patients. In 51 (58 per cent) the tumour was solitary; the number of tumours per individual ranged from 1 to 10 (median 1 (interquartile range (i.q.r.) 1·0–2·5)). Desmoids were found exclusively within the abdomen in 36 patients (41 per cent), in the abdominal wall alone in 20 (23 per cent) and at both sites in 31 (35 per cent), one of whom also had an extra-abdominal tumour. Another patient had extra-abdominal desmoids (in the chest wall and within the thorax) and abdominal wall tumours. The anatomical sites of the desmoids are detailed in *Table 1*.

The majority of desmoids (130 (78 per cent)) were clinically apparent. The remaining 36 (22 per cent) were discovered incidentally at laparotomy, in two patients preventing the planned restorative proctectomy from being carried out; in each case proctectomy and end-ileostomy was performed instead. In another patient, restorative proctocolectomy had to be abandoned and total colectomy and ileorectal anastomosis performed, and in one patient a previously unsuspected desmoid tumour rendered colectomy impossible.

Table 1 Anatomical distribution of 166 desmoid tumours

Region	*n*	Site	*n*
Intra-abdominal	83 (50)	Small bowel mesentery	73 (88)
		Pelvic retroperitoneum	6 (7)
		Transverse mesocolon	2 (2)
		Abdominal retroperitoneum	1 (1)
		Mesorectum	1 (1)
Abdominal wall	80 (48)	Surgical scar	31 (39)
		Other	49 (61)
Extra-abdominal	3 (2)	Chest wall	2 (67)
		Intrathoracic	1 (33)

Values in parentheses are percentages

One abdominal wall desmoid invaded the small bowel, resulting in a fistula. Apart from this, no serious complications occurred and the majority of abdominal wall tumours were asymptomatic. Twenty patients with intra-abdominal desmoid reported abdominal pain; complications documented in those with intra-abdominal desmoid were small bowel obstruction in 18 (27 per cent), ureteric obstruction in 16 (24 per cent), bowel perforation in six (9 per cent), enterocutaneous fistula in three (4 per cent), intestinal haemorrhage in three (4 per cent), ileoanal pouch failure in two (3 per cent) and deep venous thrombosis in one patient (1 per cent).

The diagnosis of a patient's first desmoid tumour was made at a median age of 31 (i.q.r. 22–41) years, and of desmoids overall at a median of 32 (i.q.r. 22–38) years. The age at diagnosis did not vary significantly with anatomical site.

Aetiological factors

Desmoid was diagnosed in 16 patients (18 per cent) without a history of surgery. Forty-seven individuals had undergone total colectomy and ileorectal anastomosis, ten restorative proctocolectomy, ten panproctocolectomy and five had had other abdominal operations. Desmoid tumours diagnosed after operation were identified a median of 2·4 (i.q.r. 1·5–4·4) years later. This time interval was no different for desmoids in the abdominal wall or at intra-abdominal sites.

Of the patients with desmoid tumour, 51 (58 per cent) were female and 37 (42 per cent) were male. The resulting female : male ratio of 1·4 was not significantly different from the expected ratio of 1·0. However, only nine of the 37 men compared with 27 (53 per cent) of the 51 women had more than one desmoid tumour, a statistically significant difference ($\chi^2 = 7·26$, 1 d.f., $P = 0·007$). The median age at diagnosis of desmoid tumour was significantly lower in women than in men (26 *versus* 36 years respectively; $P = 0·02$, Mann–Whitney *U* test), as was the median time since previous surgery (2·1 *versus* 2·9 years; $P = 0·01$, Mann–Whitney *U* test), although the age at prophylactic surgery did not differ according to sex.

Twenty-one (41 per cent) of the women with desmoids were nulliparous, ten (20 per cent) had had one pregnancy, 17 (33 per cent) had had two, two (4 per cent) had had three and one (2 per cent) had had four. Three women became pregnant after prophylactic surgery and went on to develop desmoid tumour within 2 years; in another, an abdominal wall desmoid grew during pregnancy. However, a further woman had had two children, her intra-abdominal desmoid remaining unchanged throughout both pregnancies. Two women who had undergone excision of abdominal wall desmoids later became pregnant; neither had recurrent or new desmoid formation on follow-up.

Desmoids developed and progressed in four women taking the combined oral contraceptive pill and in one woman receiving hormone replacement therapy. Another rapidly growing intra-abdominal desmoid became stable after oophorectomy.

Sixty-one patients (69 per cent) had no first-degree relative with desmoids, 16 (18 per cent) had one such relative and seven (8 per cent) had two. Four patients had FAP as a result of a new mutation, so had no relatives with the condition. The distribution and behaviour of the desmoid tumours in this group did not differ from those in patients with inherited mutations.

Treatment

Forty-seven desmoids were treated with NSAIDs (sulindac in all but one patient, in whom indomethacin was used); 33 continued to enlarge, while 14 stabilized or regressed. Thirty-seven patients were treated with antioestrogens (tamoxifen or toremifene); 30 progressed on treatment, while seven stabilized or regressed. The response to treatment was unrelated to sex.

Fifty-one desmoids were excised from the abdominal wall. There were no major complications or deaths, but 21 (41 per cent) recurred. Three patients had prosthetic repair of the abdominal wall (one with tantalum and two with polypropylene mesh); in none of these did the desmoid recur. Ten patients with recurrent abdominal wall desmoid underwent further excision, resulting in successful treatment in six and further recurrence in four. One of these second recurrences was successfully excised, and a second was partially excised but resulted in an enterocutaneous fistula.

In contrast, eight of the 22 patients who underwent resection of an intra-abdominal desmoid died during or immediately after operation (all due to haemorrhagic complications). Of the 14 patients who survived resection of intra-abdominal desmoid, six underwent extensive enterectomy resulting in the need for long-term total parenteral nutrition and three required blood transfusion of more than 10 units in the perioperative period. The tumour recurred in ten patients. The outcome of surgery was not influenced by sex.

Ureteric obstruction was treated successfully by stenting in three cases and by ureterolysis in a further three. Two patients underwent nephrectomy and one had ureteric reimplantation.

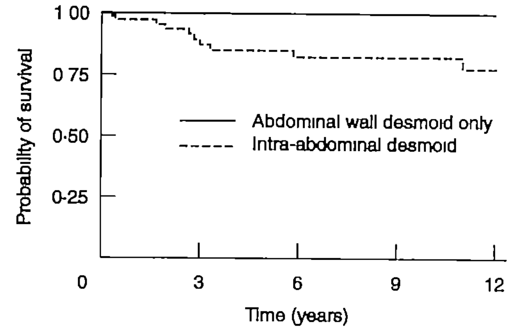
One patient was given radiotherapy to a recurrent abdominal wall desmoid, after which growth ceased. Various chemotherapeutic regimens were used: one woman was given cisplatin, doxorubicin and dacarbazine for coincidental ovarian carcinoma, but the intra-abdominal desmoid tumour continued to grow. In another patient, methotrexate and vinblastine failed to reduce tumour growth, and a third individual died from the effects of chemotherapy. In two patients, one given cisplatin and dacarbazine, and the other treated with vincristine and doxorubicin, desmoid growth ceased after chemotherapy.

Prognosis

Patients were followed for a median of 6 (i.q.r. 2·8–10·3) years. Twelve patients (14 per cent) were cured of all desmoid tumours (most by excision of abdominal wall tumours), and in five (6 per cent) all desmoids resolved spontaneously; 60 (68 per cent) continued to have desmoid tumour on follow-up. The prognosis was not influenced by sex, biopsy, occurrence before surgical trauma or status of the patient carrying a new mutation.

Overall, desmoids resulted in the death of 11 patients (13 per cent), most within 5 years of diagnosis. Ten of these had intra-abdominal disease: eight died in the perioperative period as a result of attempted resection of a tumour in the small bowel mesentery; one died with bilateral hydronephrosis and an enterocutaneous fistula; and one died from the effects of chemotherapy. A further death was due to an intrathoracic desmoid.

The Kaplan–Meier survival curve of patients with abdominal wall desmoid only and those with intra-abdominal desmoid is shown in *Fig. 1*. Survival of those



No at risk	0	3	6	9	12
Abdominal wall only	20	18	16	13	8
Intra-abdominal	67	41	31	19	15

Fig. 1 Kaplan–Meier survival curve of patients with desmoid tumour

with intra-abdominal disease was significantly worse than that of those without ($\chi^2 = 3{\cdot}93$, 1 d.f., $P = 0047$, log rank test); their 5-year survival rate was 85 (95 per cent confidence interval (c.i.) 71–92) per cent and the 12-year survival rate was 77 (95 per cent c.i. 60–88) per cent.

Discussion

The findings of this study confirm many observations from previous, smaller, series[4]. Desmoid tumours are often multiple and occur more frequently within the abdomen than in the abdominal wall; desmoids at other sites are rare in patients with FAP. The proportion of patients with multiple tumours in this series is likely to be an underestimate as many of the data predate the advent of cross-sectional imaging; many patients who present clinically with a single desmoid tumour are found to have others on computed tomography[7].

Desmoids present early in the fourth decade of life, the majority following surgery by a little over 2 years. The fact that desmoids occur in the absence of previous surgery, and that most patients with FAP undergo prophylactic surgery in their late teens, makes a definite relationship to surgical trauma difficult to confirm, but the development of desmoids in surgical scars and at laparoscopic port sites[8], and the lack of correlation between age at diagnosis of desmoid tumour and time since operation, strongly suggest that such a relationship does exist.

The sex distribution was also similar to that in previous descriptions, with a small, statistically insignificant, excess of women. However, the finding of significantly more women than men with multiple desmoids, and the fact that these arose significantly sooner after operation and at a younger age in women, support the hypothesis that oestrogens stimulate desmoid growth. The small numbers involved and lack of control data make comment regarding pregnancy and intake of oestrogens meaningless.

Abdominal wall desmoids rarely cause serious clinical problems, whereas those within the abdomen can obstruct the bowel and ureters, causing fistulation, haemorrhage and perforation, as well as making abdominal surgery difficult.

Great care must be taken in interpreting the outcome after treatment in this study. The treatments were not given as part of any prospective trial, the indications for treatment are not clear and no adequate control population exists. In particular, there is no well documented untreated group; the majority of these patients were given some treatment. However, the findings are in line with those of other reports in that the majority of desmoids treated continued to grow, suggesting a minimal, if any, effect. Biopsy did not cause the acceleration of growth that has concerned some authors[9].

The outcome of surgery was dependent on the site of the desmoid. Abdominal wall tumours had a recurrence rate of 41 per cent, but were associated with no major morbidity or mortality. Any recurrence can be treated successfully by further excision, and the use of synthetic mesh was not associated with complications. In contrast, eight of 22 patients died following operation for intra-abdominal desmoids, and the morbidity rate was significant in these patients. These data support the recommendation that operation should be the first-line treatment for abdominal wall desmoids, but should be avoided as far as possible when the tumours are within the abdomen[10]. This approach is encouraged by promising reports of the use of doxorubicin and dacarbazine chemotherapy in intra-abdominal desmoids[11]. Patients in the present series who were given cytotoxic agents did not fare well, but none received the infusion regimen currently recommended[11].

The overall outcome in these patients was similar to that described by Church[10]: the mortality rate was 13 per cent (almost all of whom had intra-abdominal desmoid) and desmoids resolved spontaneously in 6 per cent of patients. Twelve patients (14 per cent) were apparently treated successfully (although some of these tumours might have resolved spontaneously without treatment) and the majority (68 per cent) survived with stable disease.

This series is retrospective and covers a long time-span. Recently there has been increased awareness of the importance of desmoid tumours, and of potential aetiological factors. This, combined with the increasing availability of cross-sectional imaging, means that desmoids have probably been diagnosed more often in recent patients, and also that the number of desmoids has been estimated more accurately. Associated factors, such as pregnancy or the use of hormone preparations, have been recorded more reliably than in the past, but have usually not been noted in patients without desmoid tumours, making comparison impossible. Furthermore, of the 88 patients reported here, 26 had been referred to St Mark's Hospital specifically for management of desmoid tumours. It may be that some of these were particularly complex cases, biasing the results towards poorer survival.

Despite these shortcomings, this study reinforces the findings of previous series and, in particular, highlights the need for carefully designed prospective studies. Morbidity and mortality rates associated with intra-abdominal desmoid tumours, and the difficulties of management, are particularly noteworthy.

Acknowledgements

S.K.C. was supported by the Imperial Cancer Research Fund.

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Expression and clinical significance of apolipoprotein D in male breast cancer and gynaecomastia

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Background: Apolipoprotein D (Apo D) is a protein component of the human plasma lipid transport system which is present in benign and malignant human breast tissues. This study analysed the expression of Apo D in men with gynaecomastia or breast cancer, and evaluated its use as a prognostic marker in breast cancer.

Methods: Immunohistochemical expression of Apo D was examined in specimens from 15 men with gynaecomastia, two with *in situ* breast carcinoma and 68 with invasive male breast cancer. Median follow-up in patients with breast cancer was 44 months.

Results: All gynaecomastia specimens, both *in situ* carcinomas and 57 invasive carcinomas (84 per cent) stained positively for Apo D. Apo D values were significantly correlated with axillary node involvement and histological grade of the tumours. In men with breast cancer univariate analysis showed a statistical association between node status and Apo D content with relapse-free survival ($P < 0{\cdot}001$) and overall survival ($P < 0{\cdot}05$). Cox multivariate analysis showed that Apo D was a significant indicator of relapse-free survival ($P = 0{\cdot}0089$), but node status was the strongest factor able to predict both relapse-free ($P = 0{\cdot}0336$) and overall ($P = 0{\cdot}0346$) survival.

Conclusion: Apo D was expressed in gynaecomastia and a high percentage of male breast carcinomas. There was a positive association of Apo D content in male breast tumours with favourable outcome. Apo D expression was a significant independent indicator of relapse-free survival in male breast cancer.

Paper accepted 24 February 1999

British Journal of Surgery 1999, **86**, 1190–1197

Introduction

The incidence of breast cancer in men is low compared with that in women (1–1·5 per cent)[1]. However, prognostic factors, such as node status, histological grade and several markers have shown similarities in breast cancer in both sexes[2], although the prognosis in men seems generally poorer[3–6].

Apolipoprotein D (Apo D) is a protein component of the human plasma lipid transport system which was first isolated and characterized by McConathy and Alaupovic[7]. This glycoprotein has a single 30-kDa polypeptide chain. It is mainly associated with high-density lipoprotein particles[8,9]. The role of Apo D in the metabolism of plasma lipoproteins remains unclear, but it may be involved in cholesterol esterification and transport of substrates and final products of this reaction[10,11]. Apo D as a member of the lipokalin family of proteins plays a role in the binding and transport of hydrophobic substances such as cholesterol, cholesterol esters and haem-related compounds[12].

Gross cystic disease fluid protein (GCDFP) 24 (now identified as Apo D) was first detected as a component of breast cyst fluid by Pearlman *et al.* in 1973[13], and further isolated and characterized by them in 1977[14]. Studies from Silva *et al.*[15] showed that this protein was a marker of high-grade differentiation and therefore suggestive of good prognosis in female breast cancer. In 1990 this protein was characterized by Dilley *et al.*[16] as a pregnenolone- and progesterone-binding cyst protein. Balbín *et al.*[17] found that Apo D accumulated to extremely high concentrations in cyst fluid from women with gross cystic disease of the breast and proposed that it may also be involved in steroid hormone binding and transport in human mammary tissue.

Apo D has also been proposed as a marker of steroid action in human breast and prostate cancer cells[18–21]. Interestingly, the effects of steroids on Apo D expression in both types of cells are opposite to their effects on cell proliferation. This observation, together with the fact that Apo D gene expression in normal human fibroblasts seems to be specific to growth arrest, has led to the suggestion that Apo D is associated with modulation of cell proliferation[22].

Mazoujian and Haagensen[23] reported immunohistochemical staining for Apo D in female breast and sweat gland tumours. A study of the relationship between Apo D and androgen receptors in human breast[24] and prostate[25] cancer found that Apo D was androgen regulated in both cell lines *in vitro*. Moreover, these authors have shown that two similar androgen-regulated proteins, prostate-specific antigen (PSA) and GCDFP-15, are co-expressed in androgen receptor-positive breast tumours, and that PSA and GCDFP-15 immunoreactivity is dependent on the presence of androgen receptors[26].

After the unexpected finding of high concentrations of Apo D in cystic fluid from women with gross cystic disease of the breast[17], the expression of Apo D was also reported in a significant percentage of female breast carcinomas. The level of expression of Apo D was significantly associated with menopausal status and histological grade of the tumour. Higher levels of Apo D were found in postmenopausal women and in well differentiated carcinomas. In addition, low Apo D values were significantly associated with both short relapse-free and overall survival[27].

Patients and methods

Patients

This study was performed on three groups of patients. First, in order to analyse the expression of Apo D in normal male breast tissue, specimens were taken from five men who died accidentally and without previous breast pathology (aged 16, 24, 32, 40 and 56 years). Second, the expression of this protein was studied in tissues from 15 patients diagnosed with gynaecomastia (mean age 42 (range 16–69) years). Also included were two men with ductal carcinoma *in situ* (DCIS) of the breast (aged 64 and 66 years) and 68 men (mean age 68 (range 27–91) years) diagnosed with invasive breast cancer and treated between 1979 and 1995 in 17 surgical departments in Spain (listed in Acknowledgements). The clinical details of the 68 men with breast cancer are shown in *Table 1*.

Histological grade was determined according to criteria by Bloom and Richardson[28]. Node status was assessed histopathologically, and oestrogen receptor (ER) content was measured in cytosol extracts using a commercially available kit (Abbott Laboratories, Chicago, Illinois, USA).

Table 1 Apolipoprotein D immunostaining score in 68 male breast cancers

		HSCORE*		
Characteristic	No.	Mean(s.e.)	Median (range)	*P*
Age (years)				
<60	17	159·4(33)	180 (0–360)	n.s.
≥60	51	162·1(18·4)	140 (0–400)	
Tumour size				
T_1	21	147·6(26·7)	150 (0–360)	n.s.
T_2	25	184·4(27·9)	160 (0–400)	
T_3	2	280(80)	280 (200–360)	
T_4	20	135·5(29·1)	120 (0–400)	
Node status				
N_0	35	217·7(23·9)	240 (0–400)	<0·0001
N+	33	105(15·6)	120 (0–360)	
Histological grade				
I	16	230(30·6)†	240 (0–400)	<0·005
II	31	170·6(22·2)†	150 (0–400)	
III	21	95·7(27·1)	40 (0–400)	
ER status				
Positive	34	179·4(23·2)	150 (0–400)	n.s.
Negative	7	98·5(41·7)	60 (0–300)	

*Semiquantitive immunostaining score for apolipoprotein D. †$P < 0·005$ *versus* histological grade III. ER, oestrogen receptor; n.s., not significant

Breast tumours were considered ER positive if they contained more than 10 fmol per mg total protein. ER status was not available in 27 patients.

Radical or modified radical mastectomy was performed in all patients with breast cancer; postoperative locoregional radiotherapy was given to 34 patients, adjuvant systemic therapy with cyclophosphamide, methotrexate and fluorouracil to 31, and adjuvant tamoxifen to 39 patients. All patients were evaluated for disease recurrence by clinical, radiological and biological examinations every 3 months for the first 2 years, and once per year thereafter. The mean follow-up period was 44 months. Of 65 patients with follow-up, 16 developed tumour recurrence and nine of these died from recurrence. Seven other men died from causes unrelated to breast cancer.

Apolipoprotein D purification and antiserum production

Apo D was purified from breast cyst fluid of women with gross fibrocystic disease by high-performance liquid chromatography as described previously[17,29]. Antiserum against the purified protein was raised in New Zealand White rabbits[30]. The immunized rabbits were bled 6 weeks after protein injection and the resulting serum was dialysed for 24 h at 4°C against 20 mmol/l phosphate buffer, pH 7·2.

The dialysed material was chromatographed in a column of diethylaminoethyl cellulose, equilibrated and eluted in the same phosphate buffer. Finally, the immunoglobulin (Ig) G-containing fractions were collected and stored at −20°C until use.

Immunohistochemical staining

Immunohistochemical assays were performed on 5-µm formalin-fixed, paraffin-embedded tissue sections using the streptavidin–biotin supersensitive method (Biogenex, San Ramon, California, USA). Incubation with antiserum against Apo D (diluted 1:500 in 20 mmol/l phosphate buffer, pH 7·2 and 1 per cent bovine serum albumin) was performed at room temperature for 30 min. Then slides were incubated for 20 min with the second biotinylated antibody (Biogenex). The streptavidin–alkaline phosphatase complex reagent (Biogenex) was allowed to react for 20 min at room temperature and the reaction was developed with Fast Red in Tris buffer, pH 7·2, containing naphthol phosphate. Finally the slides were counterstained with Mayer haematoxylin and mounted in Aquatex (Merck, Darmstadt, Germany). The specificity of staining was determined using controls prepared by incubation of tissue sections with buffer alone or with an equal amount of IgG from non-immunized rabbits. Furthermore, immunostaining was completely abolished by preincubation of antiserum with Apo D purified from cystic fluid of women with gross fibrocystic disease as described above.

Tissue sections were scored in a semiquantitative fashion according to the method described by McCarty *et al.*[31]. Intensities were classified from 0 (no staining) to 3 (very strong staining), and 10 per cent groupings were used for the percentage of cells that stained positive. For each slide, a value designated as HSCORE was obtained after the application of the following algorithm:

$$\text{HSCORE} = \Sigma\,(\text{I} + 1) \times \text{PC},$$

where I and PC represent the intensity and the percentage of cells that stained at each intensity respectively. The reproducibility of the scoring method between two observers was greater than 90 per cent. When discrepancies were noted, differences were settled by consensus review of corresponding slides.

Statistical analysis

Analysis of differences in Apo D values between two groups of patients was performed with the Mann–Whitney *U* test. The relationship between more than two groups was evaluated by the Kruskal–Wallis test followed by the Newman–Keuls test. Survival curves were calculated using the Kaplan–Meier method[32] and compared with the log rank test[33]. Cox's regression model[34] was also used to examine several combinations and interactions of prognostic factors in a multivariate analysis. The following variables were included in the analysis: age of patients, tumour size, histological grade and node status. ER status was not included owing to the absence of data for a significant number of tumours. Selection of prognostic variables was performed with Cox's model using the stepwise regression option from BMDP software[35]. Statistical significance was established at the $P < 0{\cdot}05$ level. Results are presented as mean(s.e.).

Results

Apoprotein D expression in normal male breast tissue

Of the five men who died accidentally, only three (aged 16, 24 and 32 years) presented vestigial breast tissue; rudimentary epithelial ducts and mesenchymal components were identified without hyperplasia. All these tissues showed Apo D-positive immunostaining.

Apoprotein D expression in gynaecomastia

All tissue sections showed immunohistochemical positive staining for Apo D (*Fig. 1a*). Localization of staining was intracytoplasmic in epithelial cells in six specimens, in myoepithelial cells in four, and in both types of cells in five specimens.

Apoprotein D expression in male breast cancer

Both specimens of DCIS also showed positive staining for Apo D (*Fig. 1b*). HSCORE values for these preinvasive tumours were 140 and 300.

HSCORE values for invasive breast carcinomas ranged from 0 to 400. A total of 57 carcinomas (84 per cent) stained positively for Apo D (*Fig. 1c*); there were clear differences among them with regard to intensity and percentage of stained cells. Thus, 13 were weakly stained (HSCORE less than 100), 19 were moderately stained (HSCORE 100–200) and the remaining 25 stained strongly for Apo D (HSCORE 200–400). The mean HSCORE value was 161·6. Distribution of Apo D levels in relation to patients and tumour characteristics are listed in *Table 1*. Statistical analysis showed that Apo D values were significantly correlated with both axillary node involvement and histological grade of the tumours.

Apoprotein D immunostaining and clinical outcome

The association between Apo D and clinical outcome was evaluated retrospectively in 65 men with breast cancer and

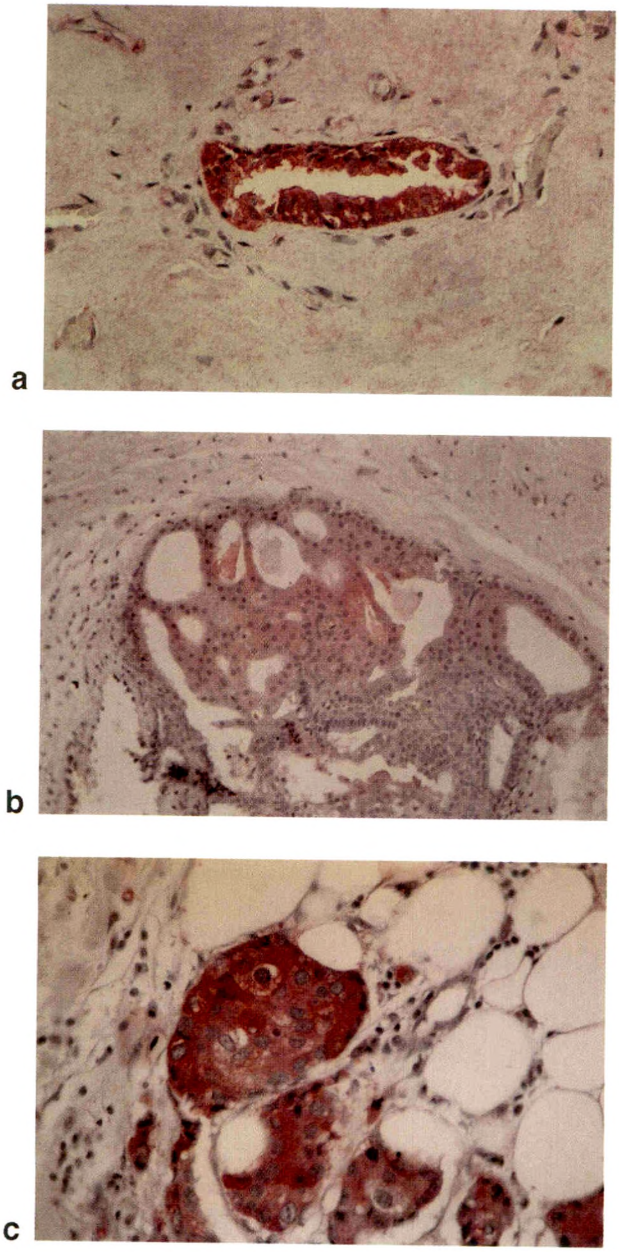
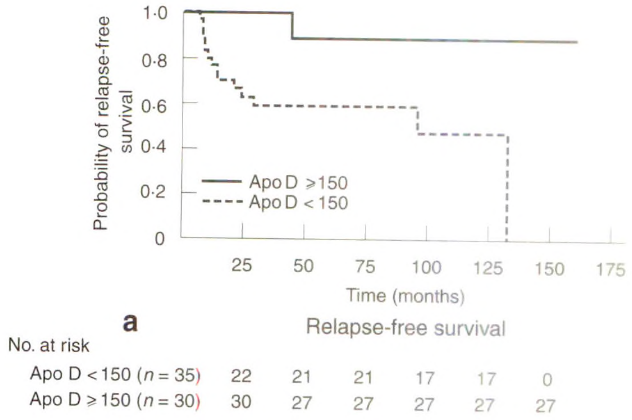
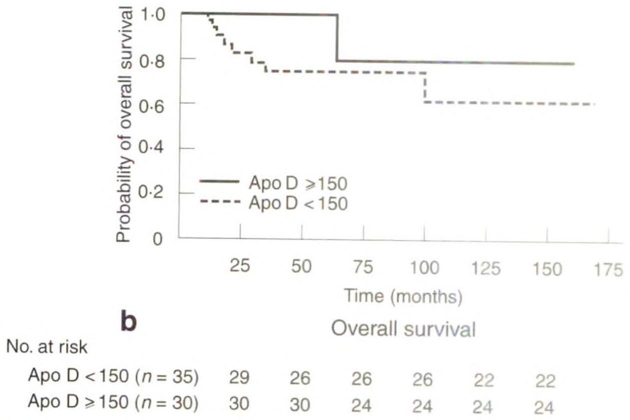


Fig. 1 Immunohistochemical staining of apolipoprotein D in **a** gynaecomastia, **b** ductal carcinoma *in situ* of the male breast and **c** male breast cancer. Tissue sections were immunostained for apolipoprotein D (1 : 500 dilution). Haematoxylin counterstain, original magnification × 100 (**a** and **b**) or × 400 (**c**)



Relapse-free survival



Overall survival

Fig. 2 Relapse-free survival and overall survival as a function of apolipoprotein D (Apo D) values in 65 patients with male breast cancer. Mean follow-up was 44 months. There were significant differences in relapse-free survival ($P = 0{\cdot}0003$) and overall survival ($P = 0{\cdot}04$) (log rank test)

without metastasis at the moment of diagnosis. First, the optimal cut-off value of Apo D able to predict relapse-free survival of the study population was defined. The analysis showed an association with relapse-free survival for HSCORE values between 100 and 160 ($P < 0{\cdot}05$ for HSCORE 100, 110 and 160; $P < 0{\cdot}001$ for HSCORE values between 120 and 150). It was determined by χ^2 analysis that an HSCORE value for Apo D of 150 was the optimal cut-off ($\chi^2 = 13{\cdot}4$, 1 d.f., $P < 0{\cdot}001$); 54 per cent of patients had low (HSCORE less than 150) Apo D values. Considering this cut-off value, relapse was confirmed in 15 of 35 patients bearing tumours with Apo D HSCORES of less than 150, but in only one of 30 with a carcinoma scoring 150 or more. Similarly, during the study, using the same cut-off point, there were eight deaths (23 per cent) from recurrence in patients with tumours scoring less than 150 and one death in a patient whose tumour had an HSCORE value of 150 or more. Differences between both relapse-free survival and overall survival curves were significant ($P = 0{\cdot}0003$ and $P = 0{\cdot}04$ respectively) (*Fig. 2*).

Univariate analysis showed that axillary lymph node involvement was also associated with relapse-free survival ($P = 0{\cdot}0009$) and overall survival ($P = 0{\cdot}0346$) in the study population (*Table 2*). Multivariate analysis according to Cox's regression model confirmed that both Apo D value

Table 2 Univariate analysis of association of apolipoprotein D with relapse-free and overall survival in 68 male breast cancers

		Relapse-free survival (%)			Overall survival (%)		
Characteristic	No.	5 years	10 years	*P*	5 years	10 years	*P*
Age (years)							
<60	18	92(6)	69(20)	n.s.	91(7)	68(20)	n.s.
≥ 60	47	63(8)	63(8)		80(7)	71(7)	
Tumour size							
T_1	21	72(12)	48(21)	n.s.	92(7)	69(20)	n.s.
T_2	25	75(10)	37(27)		80(8)	67(14)	
T_3	2	100	100		100	100	
T_4	17	64(13)	—		78(13)	—	
Node status							
N_0	35	92(2)	77(27)	0·0009	95(4)	79(14)	0·0346
N+	30	51(10)	51(10)		71(9)	59(13)	
Histological grade							
I	16	93(6)	93(6)	0·0471	88(10)	88(10)	n.s.
II	28	66(11)	66(11)		68(13)	68(13)	
III	21	65(11)	32(23)		43(31)	43(31)	
Apo D*							
<150	35	63(8)	47(12)	0·0003	74(7)	62(13)	0·04
≥ 150	30	88(10)	88(10)		80(17)	80(17)	

Values in parentheses are standard errors. *Semiquantitive immunostaining score. Apo D, apolipopotein D; n.s., not significant

Table 3 Multivariate analysis of association of apolipoprotein D with relapse-free and overall survival

	Relapse-free survival			Overall survival		
Characteristic	Relative risk	Regression coefficient	*P*	Relative risk	Regression coefficient	*P*
Node status						
N_0	0·55	1·27(0·66)	0·0336	0·49	1·53(0·8)	0·0346
N+	1·99			2·28		
Apo D*						
<150	2·65	−2·11(1·05)	0·0089	—	—	—
≥ 150	0·32			—		

Values in parentheses are standard errors. *Semiquantitive immunostaining score. Apo D, apolipoprotein D

and node status were significant independent indicators of relapse-free survival; however, only axillary node involvement was a significant independent indicator of overall survival (*Table 3*).

Discussion

The finding of Apo D expression by normal male breast tissue and gynaecomastia may suggest that Apo D may be involved in the pathophysiology of gynaecomastia or that it is a protein component of the normal (vestigial) male breast gland (after puberty, ducts and surrounding mesenchymal tissue suffer involution and atrophy in the majority of men)[36]. Previous reports have also shown Apo D expression in the normal female breast[37,38] and prostatic gland[39], but its role is unknown. Androgens upregulate the overexpression of Apo D in breast tumours. The expression of androgen receptors in female and male breast myoblastomas has very recently been reported, including two cases of gynaecomastia[40]. Proliferation of myofibroblasts (or myoepithelium) may therefore have an aetiological association with androgens.

The expression of Apo D by a significant percentage of male breast tumours of favourable outcome is in agreement with a previous report from this unit about the prognostic significance of Apo D in female breast carcinoma[27]. Considering the expression of Apo D by normal and benign breast tissue, its expression by a subset of breast tumours may indicate the existence of a high degree of differentiation. Supporting this, a significant association between both Apo D and RNA levels and well differentiated female breast tumours has been reported[27]. The present study shows a similar relationship with histological grade in male breast carcinoma.

To explain why Apo D is associated with good prognosis of tumours, its role in cell proliferation should be examined. It is known that Apo D transcription only occurs in non-proliferating and senescent human fibroblast cell cultures[22]. The presence of Apo D in breast tumours could be the consequence of cellular growth arrest and may indicate a favourable prognosis. The fact that Apo D is one of the few androgen-induced proteins in both types of cell[18–21], and that this induction coincides with an inhibition of cell proliferation[20,21], facilitates the explanation for Apo D association with tumour regression. The expression of pepsinogen C, another androgen-induced protein, has also been reported in gynaecomastia and in male breast tumours. Its expression was associated with factors of favourable outcome like histological grade and ER status[41].

Apo D production by breast carcinoma cells could reflect the existence of a complete androgenic receptor pathway. Androgens regulate breast cancer cell proliferation *in vitro*[42], but a divergent proliferative response to these steroid hormones has been demonstrated[43–45]. This may in part be due to alteration of androgen receptor genes, thus resulting in dysfunction of the androgen-regulated genes[46]. Androgen receptors as well as ERs, tumour size, node status, histological grade and Ki-67 proliferative score were significant prognostic factors able to predict relapse-free survival and hormonal response in breast cancer[47]. Hall *et al.*[24] attempted to find a relationship between androgen receptors and Apo D in human breast cancer and found androgen receptor mutations in a significant percentage of breast tumours. However, in AR-mutated cell lines, they failed to demonstrate Apo D expression as a marker of androgen receptor function *in vivo*. Further studies are needed on the complementary DNA sequence analysis of androgen receptors to confirm these mutations, the different hormonal responsiveness and the role of antiandrogens in breast cancer.

It was also remarkable in the present study that a higher percentage of male breast carcinomas expressed Apo D (84 per cent) than did invasive female breast tumours (63 per cent) in a previous study[27]. Weber-Chappuis *et al.*[48] have also reported significant differences in the immunohistochemical expression of Apo D between female (42 per cent) and male (92 per cent) breast carcinomas ($P < 0{\cdot}001$). The different expression of Apo D in breast cancer according to sex may be a consequence of the different hormonal milieu between male and female tumours.

These results suggest that Apo D in combination with other prognostic factors may help to identify men with breast cancer of favourable outcome. Apo D may represent a new prognostic factor of hormonal responsiveness which may open new perspectives for more specific treatment of human breast cancer.

Acknowledgements

The authors thank all members of the following participating clinical centres (listed in alphabetical order):

Hospital Virgen de los Lirios de Alcoy, Hospital General de Alicante, Hospital Central de Asturias, Hospital Nuestra Señora de Sonsoles de Ávila, Hospital San Agustín de Avilés, Hospital Virgen de la Luz de Cuenca, Hospital de la Marina Alta de Denia, Hospital General de Elche, Hospital de Elda, Hospital de Jove de Gijón, Hospital de Cabueñes de Gijón, Fundación Jiménez Díaz de Madrid, Hospital Ramón y Cajal de Madrid, Hospital Clínico San Carlos de Madrid, Hospital de la Vega Baja de Orihuela, Centro Médico de Oviedo and Hospital Dr Peset de Valencia.

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Contrast-enhanced colour Doppler ultrasonography in suspected breast cancer recurrence

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Background: Postoperative scarring and radiotherapy changes in the conservatively treated breast often mimic breast cancer recurrence, resulting in many unnecessary biopsies. Local breast cancer recurrence may be detected more accurately with contrast-enhanced colour Doppler imaging.

Methods: Fifty-eight women with suspected local breast cancer recurrence were evaluated prospectively by means of conventional and contrast-enhanced colour Doppler imaging before surgical biopsy.

Results: Sensitivity for the detection of breast cancer recurrence using contrast enhancement was 94 per cent (specificity 67 per cent). Contrast enhancement significantly increased overall diagnostic accuracy, from 80 to 90 per cent ($P < 0.04$).

Conclusion: Contrast-enhanced colour Doppler imaging is a highly accurate method for detecting local breast cancer recurrence. Its adoption may substantially reduce biopsy rates.

Paper accepted 4 March 1999

British Journal of Surgery, 1999 **86**, 1198–1201

Introduction

Studies comparing breast conservation with mastectomy in the treatment of small breast cancers have shown that distant disease-free and overall survival rates are equivalent[1]. However, there is a small increase in local recurrence with breast conservation surgery, 90 per cent of which occurs in the operated quadrant[2]. Furthermore, scarring and changes after irradiation produce clinical and mammographic findings that mimic local recurrence[3,4], often resulting in patients undergoing an invasive procedure to exclude recurrent breast carcinoma. Poor postoperative healing due to previous radiotherapy may increase morbidity. Annually there are 27 000 new cases of breast cancer in the UK. Ten per cent of these patients will develop local recurrence[2].

Grey-scale ultrasonography has limited ability to distinguish scar tissue from malignancy[3]. Primary breast tumours[5] have been imaged with colour Doppler ultrasonography, but since intratumoral vessels are small and Doppler signals weak its use as a diagnostic tool has so far been unsuccessful. Levovist (Schering, Berlin, Germany), a novel intravenous microbubble contrast agent for colour Doppler ultrasonography, lowers the threshold for detection of vascularity by enhancing the Doppler signal amplitude. Its use in the investigation of primary breast cancer has produced inconsistent results[5–7]. In this prospective study conventional and contrast-enhanced colour Doppler imaging were compared to determine whether they could distinguish scar tissue from local breast cancer recurrence.

Patients and methods

Patients

Fifty-eight consecutive women of median age 58 (range 41–79) years with clinical or mammographic abnormalities suggestive of local breast cancer recurrence were recruited from seven centres before scheduled breast biopsy. Patients who had undergone breast surgery within the previous 3 months were excluded. All premenopausal women underwent a urinary pregnancy test; pregnancy was not detected in any patient. The study was carried out under a CTMP (clinical trial with a marketed product) certificate from the Medicines Control Agency. All patients gave fully informed consent, as approved by each hospital's ethical research committee.

Ultrasonography

State-of-the-art sonographic units capable of power and colour-coded real-time Doppler imaging were used to evaluate all patients and recorded on S-VHS video. Standard settings for examinations both before and after

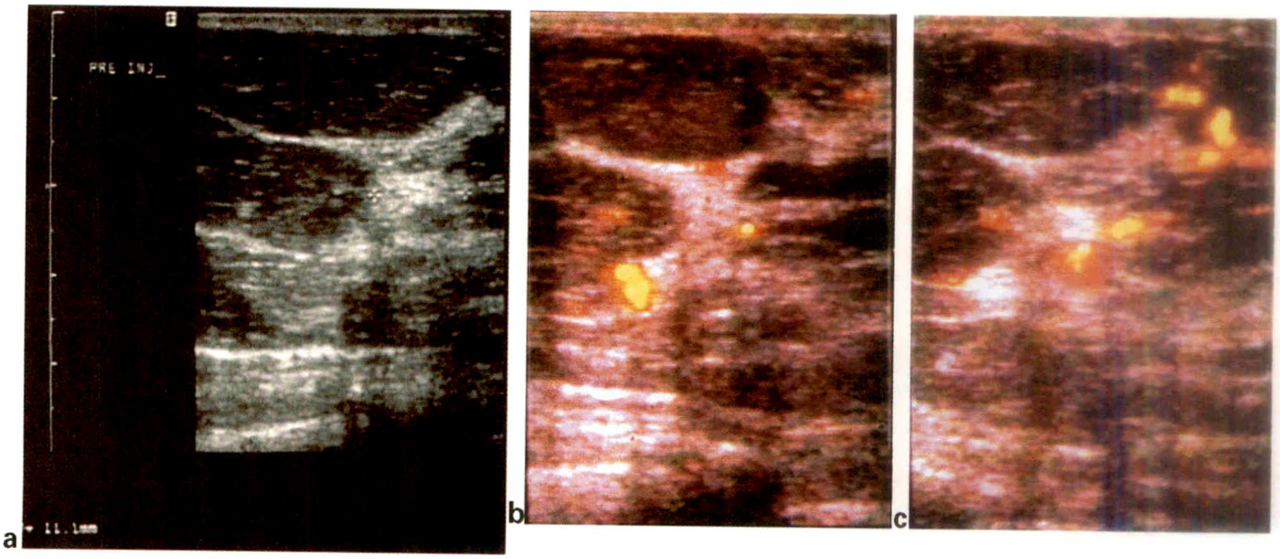

Fig. 1 Grey-scale, conventional and contrast-enhanced colour Doppler sonograms from a 56-year-old woman with diffuse breast cancer recurrence, presenting 2 years after wide local excision for a 1–2-cm (histological grade 3) invasive ductal carcinoma.
a Grey-scale image. Note the hypoechoic posterior shadowing (seen on all illustrations) suggestive of malignancy. The scale on the left-hand side shows 5-mm graduations.
b Colour Doppler ultrasonogram (in colour Doppler power) showing enhancement of malignant areas (seen as bright yellow).
c Levovist contrast-enhanced colour Doppler ultrasonogram showing increased signal enhancement in all malignant areas corresponding to posterior acoustic shadowing

the addition of contrast were: pulsed repetition frequency 800–1000 KHz, wall motion filter 50–100 Hz, velocity scale 3–5 cm/s. A thorough examination of the area of clinical or mammographic concern was made using standard grey-scale and colour Doppler ultrasonography (*Fig. 1*). The ultrasound probe was then fixed in its optimal position and a contrast-enhanced colour Doppler scan was performed following an intravenous injection of 8 ml Levovist (400 mg/ml) at a rate of 1–2 ml/s via an indwelling peripheral catheter. In some cases the Doppler gain was adjusted after injection to optimize the signal : noise ratio. Following this examination the videotapes were reviewed and lesion vascularity was graded on a scale of 0–4 (0, avascular; 1, slightly vascular; 2, moderately vascular; 3, highly vascular; 4, very highly vascular) by two experienced radiologists who reached a consensus. No other lesion characteristic was considered.

Biopsy

All patients underwent either open biopsy or a minimum of three needle-core (Tru-cut, Travenol Laboratories, Thetford, UK) biopsies. Experienced breast pathologists reported all biopsies. Slides (or sample blocks) were forwarded blindly to a reference centre in the UK.

Statistical analysis

The number of patient scans with vascularity grades above and below each cut-off point (grade less than 0, 0–1, 1–2, 2–3, 3–4 and greater than 4) were counted. Scans with vascularity grades higher than the cut-off point being considered were assumed to be malignant (i.e. they represented the true positives plus any false positives), and scans with vascularity grades falling below the cut-off point were assumed to be benign (i.e. true negatives plus any false negatives). Using the final histological diagnosis at the end of the study, sensitivity and specificity were determined at each cut-off point (*Table 1*). Receiver–operator characteristic (ROC) curves were constructed using these values (*Fig. 2*). The area underneath each ROC curve represented overall diagnostic accuracy (a combined measure of sensitivity and specificity) and was calculated using the Wilcoxon statistic[8]. Kendall's τ[9,10] was used to compare both these areas to determine whether there was a true difference in accuracy between diagnostic tests. This method correctly compared paired ratings, as patients were able to act as their own controls. The overall difference in diagnostic accuracy between conventional and Levovist contrast-enhanced Doppler imaging was assessed for statistical significance.

Results

Sixteen patients (28 per cent) had histologically confirmed local breast recurrence (15 invasive carcinomas, one ductal carcinoma *in situ*). There was full agreement between

Table 1 Sensitivity, specificity and false-positive error rate across vascularity grades 0–4 before and after contrast enhancement

	Cut-off point (vascularity grade)					
	<0	0–1	1–2	2–3	3–4	>4
Precontrast						
True positive	16	12	5	2	0	0
False positive	42	8	2	0	0	0
True negative	0	34	40	42	42	42
False negative	0	4	11	14	16	16
Sensitivity (%)	100	75	31	12	0	0
Specificity (%)	0	81	95	100	100	100
False-positive error rate (%)	100	19	5	0	0	0
Postcontrast						
True positive	16	15	12	9	2	0
False positive	42	14	4	2	0	0
True negative	0	28	38	40	42	42
False negative	0	1	4	7	14	16
Sensitivity (%)	100	94	75	56	12	0
Specificity (%)	0	67	91	95	100	100
False-positive error rate (%)	100	33	9	5	0	0

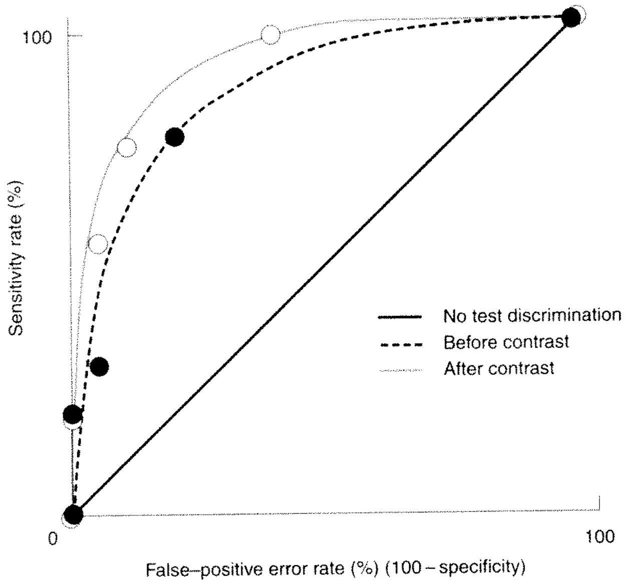

Fig. 2 Receiver–operator characteristic curves before and after contrast enhancement. The points shown correspond with values in *Table 1*. The postcontrast curve occupies 90 per cent of the graph area (i.e. has an overall diagnostic accuracy of 90 per cent) compared with an overall diagnostic accuracy of 80 per cent precontrast

reporting pathologists in all cases *(Table 1)*. Equal numbers of patients underwent open and core biopsies.

The overall diagnostic accuracy of the test was significantly increased with Levovist compared with conventional Doppler imaging (90 *versus* 80 per cent, $P < 0.04$) *(Fig. 2)*. Sensitivity for the detection of breast cancer recurrence using contrast enhancement reached 94 per cent (specificity 67 per cent) at the 0–1 (avascular–vascular) cut-off point *(Table 1)*.

Discussion

The past 25 years have seen great advances in the surgical treatment of small breast cancers, with mastectomy having largely been replaced by breast conservation surgery. Mammography and clinical examination have limited ability to detect local breast cancer recurrence accurately, due in part to surgical scarring and changes after irradiation[3,4], which has resulted in a large number of unnecessary benign biopsies.

An inexpensive, accurate and reliable method to distinguish local breast recurrence from postoperative scar tissue would be of great clinical value. The ROC curves demonstrate that colour Doppler imaging before and after contrast enhancement can discriminate recurrence since both curves lie far to the left of a hypothetical straight line representing a diagnostic test that infers no benefit (*Fig. 2*). Colour Doppler vascularity is therefore a discriminator of malignancy in breast recurrence. The relative area under the ROC curve for contrast-enhanced ultrasonography (90 per cent) is greater than that for conventional colour Doppler imaging (80 per cent). The difference between these areas suggests that contrast-enhanced colour Doppler ultrasonography is significantly better ($P < 0.04$) than conventional colour Doppler imaging at discriminating malignancy in suspected recurrence. These results appear to be consistent with those of Kedar *et al.*[6] in their evaluation of benign and malignant primary breast carcinomas. Their study compared the morphological characteristics of vessels rather than overall vascularity before and after contrast enhancement using paired ROC curve analysis. This provided a similar increase in diagnostic accuracy, from more than 80 per cent to more than 90 per cent.

Given the highly accurate nature of these findings and recent major improvements in three-dimensional colour Doppler imaging[11], colour Doppler ultrasonography might have wider applications such as in screening for primary breast cancer.

Magnetic resonance imaging (MRI), the best available imaging modality for the detection of breast cancer recurrence, is reliant upon tumour vascularity and vascular permeability[12,13] for contrast enhancement. MRI has a sensitivity of 93–100 per cent and a specificity of 83–88 per cent for the detection of local recurrence[14]. The optimal sensitivity (94 per cent) and specificity (67 per cent) of Levovist in the present study (vascularity grade 0–1, avascular–vascular cut-off point) is comparable to that for MRI[15,16]. Contrast-enhanced colour Doppler imaging has the advantage of being inexpensive, quick and easy to perform.

Contrast-enhanced colour Doppler vascularity can act as a powerful discriminator of malignancy in patients with suspected breast cancer recurrence. Using this method, biopsy could be limited to vascular breast lesions. The adoption of this selective policy may substantially reduce biopsy rates in patients with suspected breast cancer recurrence.

Acknowledgements

The authors thank Lynda Stevens from the Department of Epidemiology and Health, University College, London, for advice with the statistical components of this paper.

This work was sponsored by Schering Healthcare, Berlin, Germany.

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Abnormal neurophysiology in patients with oesophageal motility disorders

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Background: The pathology of oesophageal motility disorders is poorly understood. Oesophageal manometry provides only a descriptive assessment of luminal pressure changes. This study applied the investigative methods of the neurophysiologist to gain insight into the pathophysiology of these disorders.

Methods: Twelve healthy volunteers and 28 patients with oesophageal motility disorders underwent oesophageal manometry and balloon stimulation studies. Cortical evoked potentials (CEPs) in response to electrical stimulation of the oesophagus and oesophageal motor evoked potentials (MEPs) to transcranial magnetic stimulation of the cerebral cortex were recorded.

Results: Only two patients had abnormalities with a primary defect in muscle function. Fifteen had abnormal responses to balloon stimulation with normal CEPs and MEPs, suggesting a defect in the intrinsic nerves of the oesophagus. Five with achalasia did not respond to balloon stimulation and had abnormal CEPs and MEPs, suggesting widespread neural defects. The remainder had a variety of abnormal responses suggesting possible defects in receptor sensitivity, central processing or sensory neuropathy. There was no correlation between the manometric diagnosis and abnormal neurophysiology, except in patients with achalasia.

Conclusion: Neurophysiological testing suggests that oesophageal motility disorders are most commonly due to a variety of neural defects.

Paper accepted 26 April 1999

British Journal of Surgery 1999, **86**, 1202–1206

Introduction

Abnormal oesophageal motility implies a disturbance of neuromuscular function. Degeneration of the intrinsic nerves was first reported in achalasia by Rake in 1927[1]. There is also some evidence that the extrinsic nerves[2] and vagal nuclei[3] may be abnormal in achalasia. Abnormalities in the vagus nerves have been reported in diffuse oesophageal spasm[4]. Oesophageal manometry is commonly used to diagnose oesophageal motility disorders and provides the basis of the currently accepted classification system[5], although the majority of patients with abnormal manometry have non-specific disorders[6,7]. Cohen[8] has criticized the present classification system stating that 'advancement in the understanding of the oesophageal motility disorders is going to require the development of new experimental techniques that are suitable for human investigation'.

In recent years a variety of neurophysiological techniques has been adapted for use in the oesophagus. Oesophageal sensation can be assessed using cortical evoked potentials (CEPs) in response to either mechanical[9,10] or electrical[11,12] stimulation. These tests have been used in patients with non-cardiac chest pain[11,13] but have not yet been used in patients with primary oesophageal motility disorders. Oesophageal motor pathways can be assessed with transcranial magnetic stimulation of the cerebral cortex with simultaneous oesophageal electromyography[14].

The object of the present study was to apply the investigative tools of the neurologist to the oesophagus to identify abnormalities that might provide insight into the pathophysiology of oesophageal motility disorders.

Patients and methods

Subjects

Twelve healthy asymptomatic volunteers (eight men) of median age 29 (range 20–72) years and 28 patients (12 men) of median age 38 (range 17–67) years with primary oesophageal motility disorders were studied. No volunteer was diabetic, had any gastrointestinal, cardiorespiratory or neurological symptoms or was taking regular medication. Twenty-one patients had dysphagia and ten had non-cardiac chest pain of at least 6 months' duration. Only three patients had non-cardiac chest pain as the only symptom. All patients had upper gastrointestinal endoscopy to exclude structural disease or oesophagitis. A bread barium swallow examination was performed in 24 patients. All patients had a normal 24-h oesophageal pH study with a normal DeMeester score and had no symptomatic response to a therapeutic trial of a proton pump inhibitor. All underwent oesophageal manometry, graded intraoesophageal balloon distension and electrical stimulation with simultaneous CEP recording. All volunteers and 22 patients had transcranial magnetic stimulation to identify the motor evoked potential (MEP).

Oesophageal manometry and balloon distension

Water-perfused oesophageal manometry was performed with a seven-channel polyvinyl catheter 4·0 mm in diameter (Wilson Cook, Letchworth, UK). The recording orifices were positioned 5, 10 and 20 cm from the catheter tip. A 2-cm length of silicone tubing (Medasil, Leeds, UK) was positioned 15 cm from the catheter tip to form a balloon. Oesophageal manometry and balloon distension studies were performed using established protocols[15,16]. The midpoint of the balloon lay 6 cm above the lower oesophageal sphincter (LOS). The balloon was inflated with air until patients described definite sensation and manometric events were then measured 5 cm proximal and distal to the balloon.

Electrical stimulation and recording of cortical evoked potentials

The balloon catheter was removed before intraoesophageal electrical stimulation. Electrical stimulation was performed using a 3·5-mm external diameter solid-state manometry catheter (Gaeltec, Isle of Skye, UK) with a pair of bipolar ring electrodes placed 5 cm above the LOS.

CEPs were recorded using two silver–silver chloride scalp electrodes positioned at Cz (vertex) and the ear lobe in accordance with the 10–20 international system for electroencephalography[17]. The scalp was cleansed with 95 per cent alcohol so that each electrode had an impedance of less than 5 kohm. The recording electrodes were connected to a commercially available brain mapper (Dantec Concerto; Dantec Electronik, Skovlunde, Denmark) which displayed the electrical activity as it occurred and stored the data for later analysis. Electrical stimulation was also controlled by the brain mapper. Filter settings were 1 Hz (high pass) and 120 Hz (low pass), and a 50-Hz notch filter was used to eliminate interference from the mains electrical supply if needed. An artefact rejection facility was used to reduce contamination from eye blinks and swallowing. Subjects were semirecumbent, asked to attend to the stimulus and minimize eye movement. The recording epoch was 500 ms after the onset of each stimulation. Two runs of 50 stimuli were performed at an intensity producing definite sensation at a frequency of 0·2 Hz. The scalp electrical activity was averaged so that background random cerebral activity was reduced and the oesophageal CEP activity became conspicuous. Sham stimulations were also performed with no current passing through the catheter.

Transcranial magnetic stimulation was performed with a commercially available magnetic stimulator (Dantec). This consisted of a 90-mm circular coil capable of producing a stimulus intensity of up to 2·0 T. The coil was placed at right angles to the subject's head over the vertex and triggered by hand. Oesophageal electromyographic recordings were made on a Counterpoint system (Dantec) which displayed the activity and stored it for subsequent analysis. The catheter was positioned so that the upper electrode pair was 2 cm below the lower margin of the upper oesophageal sphincter as confirmed by manometry. The Counterpoint was triggered to record electromyographic activity in the oesophagus for 300 ms following stimulation. Filters of 20 Hz and 2 kHz were used and a ground electrode was attached to one forearm. Stimulation was increased in 0·1-T increments until an oesophageal MEP was detected.

Data analysis and definitions

Oesophageal manometry enabled the following manometric diagnoses to be made: achalasia, diffuse oesophageal spasm (DOS), nutcracker oesophagus and non-specific motility disorder (NSMD)[5].

Intraoesophageal balloon distension gave findings reported as: normal, failure of distal inhibition (FDI), spasm or unresponsive[18].

CEPs were defined by stimulation threshold (intensity required to produce definite sensation) and latency (time from onset of stimulation to the peak of the first deflection).

Oesophageal electromyographic responses to cortical stimulation were defined by stimulation threshold (intensity required to produce a MEP), latency (time from the onset of stimulation to the peak of the first electromyographic response) and amplitude (maximum interpeak voltage).

Results

All volunteers had normal oesophageal manometry findings and a normal response to balloon distension. The patients had the following manometric diagnoses: achalasia (five), DOS (four), nutcracker oesophagus (two), NSMD (eight) or putative myopathy with contraction amplitudes of less than 30 mmHg (two). Seven patients had normal manometry findings, but had a definite history of dysphagia and showed abnormal and symptomatic bread bolus passage during a bread barium swallow. The findings were interpreted by the radiologist as ineffective primary or secondary peristalsis (four patients), pooling or retrograde movement of barium (two) and abnormal oesophageal contractions (one). One of the patients with low-amplitude peristaltic contractions had diffuse visceral myopathy previously documented by histological analysis of an extensive small bowel resection specimen. The second patient with low-amplitude contractions had a diffuse skeletal myopathy of unknown cause.

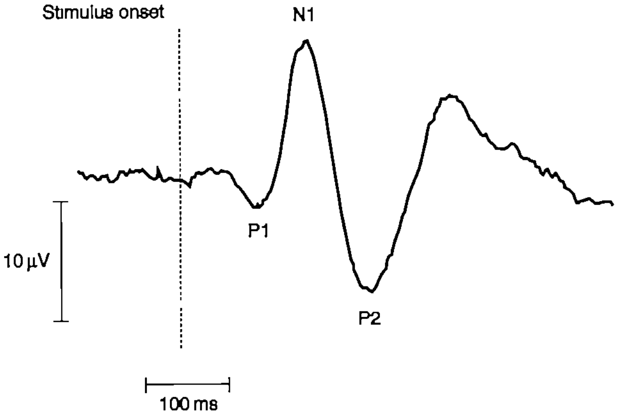

Fig. 1 Oesophageal cortical evoked potential from a healthy subject. Positive potentials are displayed as a downwards deflection

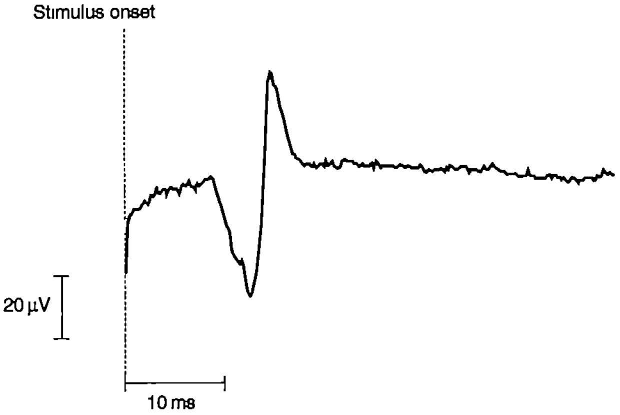

Fig. 2 Oesophageal motor evoked potential from a healthy subject

Intraoesophageal balloon distension

The patients had the following responses to balloon distension: normal (eight), FDI (five), spasm (five) and unresponsive (ten). Some patients with the same manometric diagnosis had different responses to balloon distension. The two patients with myopathies demonstrated a low-amplitude response. All five patients with achalasia were unaware of balloon distension and showed no contractile response at maximum balloon volume.

Cortical evoked potentials

A normal CEP response is shown in *Fig. 1*. In normal volunteers the median threshold to electrical stimulation was 32 (range 26–36) mA. The median latency of the P1 component of the CEP, which is thought to represent the first cortical response to the stimulus, was 111 (93–124) ms at a definite but non-painful sensation. The CEP responses observed in the patients were as follows: normal stimulus threshold and latency (19 patients), decreased stimulus threshold (two) and absent (seven).

Magnetic simulation and motor evoked potentials

A normal MEP response is shown in *Fig. 2*. In normal volunteers the median stimulus threshold for the MEP was 1·4 (range 0·8–1·6) T. The greatest MEP responses were obtained in volunteers and patients at 1·8 T. The MEP responses in the 22 patients were normal (17 patients), increased stimulus threshold (two), increased stimulus threshold with increased MEP latency and decreased amplitude (two), and absent (one). The abnormal responses were in patients with achalasia.

Sites of neuromuscular abnormality

By combining the results of all the tests it was possible to postulate a likely site or sites of the neuromuscular abnormality for each patient (*Table 1*). The results for achalasia were relatively uniform, but there was a poor correlation between the manometric findings and neurophysiological tests for the other conditions.

Discussion

Understanding the pathophysiology of oesophageal motility disorders may be a prerequisite for developing more rational and effective treatment. In the past 15 years

Table 1 Test results and postulated site of pathology

Abnormal physiology	*n*	Clinical diagnosis	Postulated site of pathology
Spastic* to IOBD, normal CEP and MEP	10	Nutcracker (1), DOS (3), NSMD (2), dysphagia with normal manometry (4)	Intrinsic nerves
Unresponsive to IOBD, normal CEP and MEP	5	DOS (1), NSMD (2), dysphagia with normal manometry (2)	Intrinsic nerves
Unresponsive to IOBD, absent CEP and/or MEP	5	Achalasia (5)	Complete denervation
Low-amplitude oesophageal contraction to swallow and IOBD, normal CEP and MEP	2	Visceral myopathy (1), skeletal myopathy (1)	Muscle
Normal IOBD and MEP, reduced stimulus for CEP	2	Nutcracker (1), NSMD (1)	Receptor sensitivity or central processing
Normal IOBD with normal CEP and MEP	2	NSMD (1), dysphagia with normal manometry (1)	?Central processing
Normal IOBD and MEP with absent CEP	2	NSMD (2)	?Normal or neuropathy

IOBD, intraoesophageal balloon distension; CEP, cortical evoked potential; MEP, motor evoked potential; DOS, diffuse oesophageal spasm; NSMD, non-specific motility disorder. *Spastic responses include those with failure of distal inhibition

oesophageal manometry has developed as a tool to distinguish normal and abnormal motility, and to provide a descriptive classification of these abnormalities. The neural control of oesophageal motility is now much better understood than formerly since the study methods of the neurologist have been adapted to the human gastrointestinal tract[10–14]. Thus far CEPs have been used to study patients with non-cardiac chest pain and it has been suggested that there may be abnormal central sensory processing[10].

The present study is the first application of a comprehensive range of oesophageal and neurophysiological tests to patients with symptomatic oesophageal motility disorders. It is also the first application of the technique of transcranial magnetic stimulation to oesophageal disorders. The tests are technically demanding for investigator and subject alike, and there must always be some reservation about the interpretation of early results from complex technology. They are certainly not suitable for routine clinical application at present. Nevertheless the authors believe that it is possible to postulate sites of neuropathology that may be amenable to further study.

Achalasia is the only motility disorder that is known to result from a degenerative neural disorder[1]. This study has confirmed the presence of severe and widespread neural abnormalities in achalasia. It was particularly interesting to find abnormal CEP and MEP responses that might indicate evidence of long-tract neural degeneration. This may support the pathological findings of Cassella *et al.*[2,3]. The patient with known visceral myopathy demonstrated abnormalities consistent with an isolated smooth muscle disorder. The other patients displayed a variety of abnormalities. These ranged from changes in sensory thresholds to an inability to detect a CEP. The former may be due to abnormal receptor sensitivity, abnormal spinal or cortical processing, or possibly to a psychological abnormality. Inability to record a CEP might indicate a more widespread neurological disorder, perhaps of similar origin to achalasia.

It is important to develop new techniques if the challenge of understanding motility disorders is to be met. In particular, identifying a cause of abnormal motility outside the oesophagus may redirect treatment modalities from those that crudely increase or reduce smooth muscle contractility by medical or surgical means.

In the context of clinical neurology, the neurologist does not attempt to make a diagnosis simply by measuring the strength of a muscle as this gives limited information. It is important to study long-tract and short-tract innervation as well. The gastroenterologist is thus at a considerable disadvantage if all that can be done is to measure how strongly the oesophagus contracts. The neurophysiological tests described are laborious and technically demanding. However, they are not unduly uncomfortable and the techniques are improving rapidly. It is impossible to be dogmatic at present about the significance of the findings, but they indicate that further detailed study of neuromuscular performance is required in those suffering from oesophageal motility disorders.

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Postoperative peritonitis originating from the duodenum: operative management by intubation and continuous intraluminal irrigation

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Background: The mortality rate associated with postoperative peritonitis remains high, especially when the source of infection cannot be eradicated. Such is the case with peritonitis arising from the duodenum, as primary closure is futile and intubation alone may be followed by local complications.

Methods: Forty-nine consecutive patients with postoperative peritonitis originating from a duodenal leak and a mean Acute Physiology And Chronic Health Evaluation II score of 17·7 were treated according to the following procedure: a three-channelled spiral drain was inserted through the leak and extraluminal drains were placed near the duodenal defect. Intraluminal irrigation was undertaken immediately through the infusion channel of the spiral drain.

Results: Eleven patients died and 26 suffered complications. The mean duration of intubation was 21 days.

Conclusion: Intubation with intraluminal irrigation has proved effective in a homogeneous group of patients with peritonitis due to duodenal leakage.

Paper accepted 23 April 1999

British Journal of Surgery 1999, 86, 1207–1212

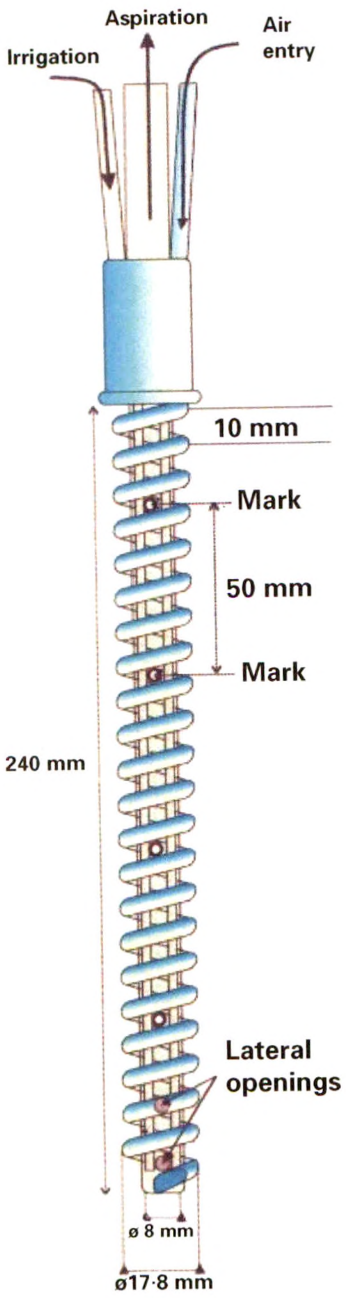
Introduction

Postoperative peritonitis requiring reoperation is still associated with a mortality rate of approximately 50 per cent[1–4]. The main prognostic factor associated with treatment is the ability to control the source of infection[5–8]. The latter is particularly difficult when the contaminating source is in the upper gastrointestinal tract and therefore not amenable to exteriorization as a stoma. No technique in this situation has proved satisfactory[9–11].

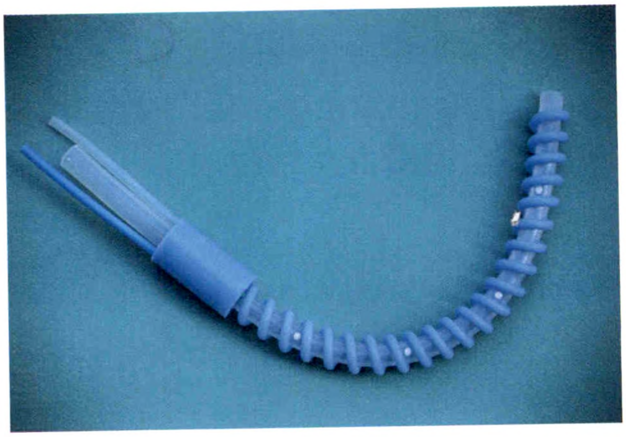
In an attempt to address this critical point, a technique of intubation and continuous intraluminal irrigation was developed, as first reported in 1984[12,13]. This technique has subsequently been modified with the incorporation of a new drain (three-way spiral silicone catheter, Saint-Antoine Type; Laboratoire Eugédia, Chambly, France). The present paper reports the updated results of this technique in a homogeneous group of patients with postoperative peritonitis originating from the duodenum.

Patients and methods

In the period 1980–1995, 385 consecutive patients were admitted to the surgical digestive intensive care unit, Hôpital Saint-Antoine, for postoperative peritonitis requiring a relaparotomy, i.e. excluding single abscesses accessible to percutaneous or elective surgical drainage and enterocutaneous fistula without extensive peritoneal infection. The source of infection was located in the upper gastrointestinal tract in 116 patients, of whom 86 required intubation. This paper reports 49 patients with a duodenal leak as the source of infection, either isolated or associated with other lesions, treated with this technique. Thirteen of these patients have been included in previous reports[12,13]. There were eight women and 41 men, of median age 48 (range 19–79, mean 48) years. Nine patients were operated initially in this department (primary cases), nine were referred from other institutions after the first operation (secondary cases) and 31 were referred after failed surgical treatment of postoperative peritonitis in the original institution (tertiary cases). Medical co-morbidity was present in 17 patients: cardiac disease ($n = 9$), alcoholism ($n = 6$), chronic respiratory insufficiency ($n = 6$), extradigestive cancer ($n = 2$) and miscellaneous disease ($n = 6$). The median time between the initial operation and treatment in this department was 16 days. Referred patients were operated in this department on the day of admission. For the tertiary referrals, the median time between the last



a Dimensions



b Photograph

Fig. 1 Three-channel spiral silicone catheter. **a** Diagram of detail and dimensions. **b** Photograph

operation at the referring centre and that performed in this department was 6 (range 1–78, mean 10) days. The mean Acute Physiology And Chronic Health Evaluation (APACHE) II score, measured within 24 h of admission to this intensive care unit, was 17·7 (range 11–31).

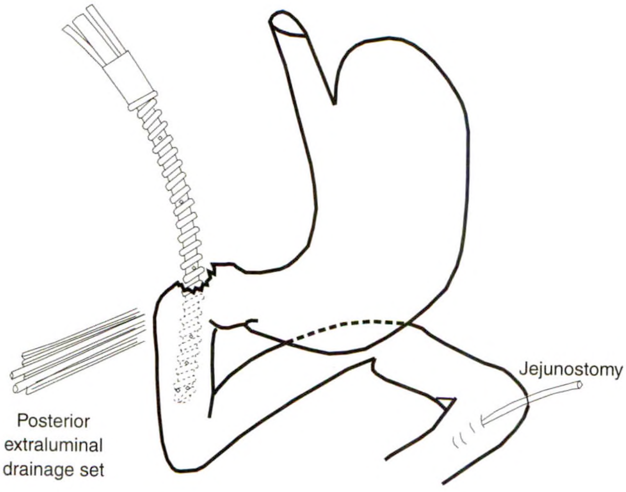
In the same period, 43 patients with a duodenocutaneous fistula but no extensive sepsis were treated. They are excluded from this study.

Surgical procedure

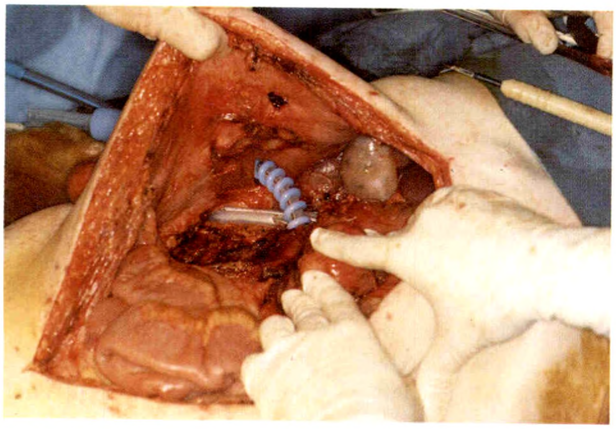
The surgical strategy includes a laparotomy for complete exploration and lavage of the abdominal cavity, eradication of all sources of infection, drainage of dependent areas, jejunostomy for continuous enteral nutrition and primary abdominal wound closure. Intubation is performed as follows: a spiral drain (*Fig. 1*) is inserted into the duodenum through the leaking site and positioned in the lumen, its intraluminal end directed towards the ampulla of Vater.

Two situations are commonly encountered, lateral or end intubation of the duodenal leak. Two sets of extraluminal drains, each made from two soft silicone tubes (one 30 Fr, one 16 Fr in each set) and a corrugated drain are placed anterior and posterior to the leakage site, with a negative pressure of 30 cmH_2O by suction applied to the 30-Fr tubes. The extraluminal drainage tubes collect the fluid that leaks between the spiral drain and the edge of the duodenal defect (*Fig. 2*). A capillary (Mikulicz) drainage unit[14] is placed on the anterior aspect of the lesser curvature and exteriorized through the upper part of the incision. Associated lesions of the bowel are exteriorized as temporary stomas[15].

The abdominal wall is closed primarily without excessive tension, either with a conventional technique or with relaxation incisions[16]. Infusion through the spiral drain begins at the end of the operation, at a rate of 2000 ml per 24 h, with a formula containing thrombin 2500 Mellanby units, tranexamic acid 500 mg and rifampicin 50 mg per litre of isotonic saline. The aim is to obtain an isoionic and isotonic environment in the duodenal lumen and its surrounding area, diluting the gastroduodenal secretions by about three times.



a Duodenal intubation



b Operative photograph

Fig. 2 **a** Intubation and continuous intraluminal irrigation in a lateral duodenal leak. The anterior extraluminal drainage set is not represented.
b A patient with intubation of a duodenal leak showing the spiral drain and an extraluminal drainage set

Postoperative management

In the first 15 days, most of the discharge is collected through the extraluminal drains. Thereafter, the intraluminal unit (i.e. the spiral drain) usually 'takes over', collecting most of the fistula output, thus allowing the other drains to be removed gradually. At a mean of 21 days, the spiral drain can be withdrawn and replaced by a 12-Fr silicone drain which is progressively removed to permit closure of the fistula. Enteral nutrition is supplied via a jejunostomy.

Results

In all cases the source of infection was duodenal leakage. In ten patients an associated source of infection was present: small bowel ($n = 5$), bile duct ($n = 3$), colon ($n = 1$) and colon and small bowel ($n = 1$). Peritonitis was either multilocular or generalized. The effluent was located predominantly in the supracolic compartment in 21 patients, in the infracolic compartment in two and was equally distributed in both in 26 cases. The mechanism responsible for the duodenal lesion was a leak from a suture line in 43 cases, tissue necrosis in one and operative trauma in five. Culture of the peritoneal fluid was positive in all patients: one micro-organism was isolated in 16 cases and polymicrobial infection was present in 33.

Duodenal intubation was lateral in 32 cases and end in 17. In the presence of another source of infection, an additional procedure was performed: stoma of the small bowel ($n = 6$) or colon ($n = 2$), or biliary intubation ($n = 7$). The abdominal wall was closed with a conventional technique in 19 patients and with relaxation incisions[16] in 30. In ten patients, a Vicryl (Ethicon, Edinburgh, UK) mesh was placed on the bowel loops.

Continuous enteral nutrition via the jejunostomy was started a median of 6 (range 3–15) days after the operation. The median duration of enteral nutrition was 75 (range 20–140) days.

Eleven patients died. Of these, seven died within 20 days of operation. In all cases of early death, the patient had multiple organ failure (three or more organs) before operation. In three of the four late deaths, pre-existing disease was prominent, namely advanced carcinoma ($n = 2$) and recent myocardial infarction associated with chronic renal insufficiency ($n = 1$). The mortality rate increased with age (*Fig. 3*) and APACHE II score (*Fig. 4*).

Twenty-six patients had one or more complications. In four patients recurrent abscesses were observed, of which three required reoperation, with no death. One patient died without reoperation (abscesses were found at autopsy). At reoperation for recurrent abscess, a new lesion was found to explain the sepsis in two patients: pancreatic necrosis in one and a colonic fistula in the other. An enterocutaneous fistula was observed in three patients, of the small bowel in two and colonic in one. There were seven cases of abdominal wall complications: abscess ($n = 1$), partial dehiscence that did not require reoperation ($n = 3$) and evisceration requiring reoperation ($n = 3$).

Thirteen patients underwent reoperation, in five cases because of suspicion of recurrent infection, for intraperitoneal haemorrhage in four, wound dehiscence in three and small bowel obstruction in one.

In 32 patients the duodenal fistula created by the procedure healed spontaneously, at a median time of 39 (range 19–120) days. In six cases operative closure was required, either direct closure ($n = 3$) or duodenojejunostomy ($n = 3$). Seven other patients underwent reoperation for

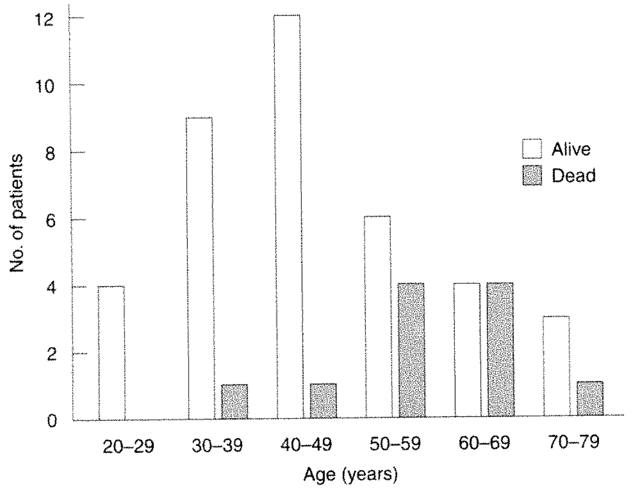


Fig. 3 Numbers of survivors and deaths according to age

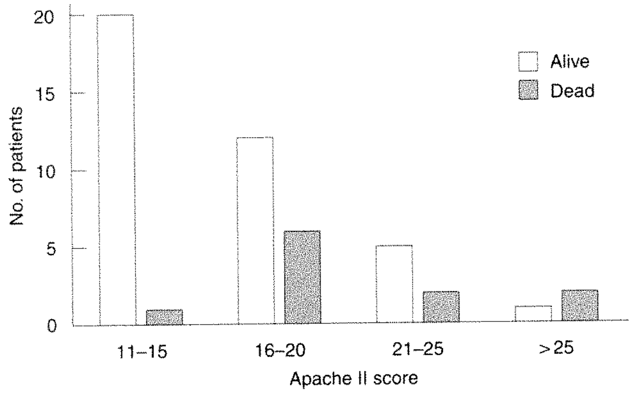


Fig. 4 Numbers of survivors and deaths according to Acute Physiology And Chronic Health Evaluation (APACHE) II score

closure of a stoma (six ileostomies, one colostomy). There was no death or complication after these delayed procedures.

The median time of hospitalization (including restoration of continuity or late fistula closure) in survivors was 100 (range 32–255) days.

Discussion

This study focused on a homogeneous group of patients suffering from postoperative peritonitis caused by leakage from the duodenum. There are two reasons for identifying this category of patient. First, a clear distinction should be made between intra-abdominal sepsis and external duodenal fistula; the latter is the result of exteriorization of the duodenal leak, with a variable degree of intra-abdominal sepsis, and is amenable to conservative treatment in the majority of cases[17–19]. Such patients are excluded from the present study, which is directed toward the more life-threatening condition of generalized postoperative peritonitis due to duodenal leakage. Second, it is important to differentiate postoperative peritonitis from other forms of secondary peritonitis, either spontaneous or post-traumatic. This is because patients with postoperative peritonitis are exposed to three successive pathological episodes: the primary disease, the first operation and the infection that follows, these together contributing to the syndromes of systemic inflammatory response, sepsis and multiple organ dysfunction. The importance of considering postoperative peritonitis separately has been stressed by many authors[20,21]. Bohnen *et al.*[22] emphasized the severity of postoperative peritonitis. Meakins *et al.*[23] proposed the addition of an anatomical classification to the evaluation of the severity of illness using the APACHE II score; postoperative peritonitis was singled out as a separate entity. This distinction between other forms of peritonitis and postoperative peritonitis is further justified by the high mortality rates reported in series focused on the subject, which average 50 per cent[1,4,24–26], well above the usual mortality rate associated with peritonitis which averages 20 per cent[20].

Postoperative leakage from the upper gastrointestinal tract represents a specific technical challenge to the surgeon, as exteriorization of the source of infection is impossible. This technical problem is critical as control of the source of contamination is a key determinant of outcome[6,8,21,27].

The present results are difficult to evaluate as, to the authors' knowledge, no other paper specifically addressing peritonitis arising from duodenal leakage has been published; observations collected from practice and more general publications indicate that this condition is associated with a mortality rate greater than 50 per cent[1–5,7,11,20,21,28–30]. The present results represent an improvement when compared with historical controls from this institution treated with conventional measures. An earlier report[13] describes 39 patients treated by conventional techniques with 26 deaths, and 46 by the new type of management with ten deaths.

Other techniques have been described in the management of postoperative duodenal leakage. Immediate suture of any oedematous and necrotic intestinal defect almost invariably fails[28,31], as does resection and construction of a new anastomosis[11,15,28]. Reports of intubation alone of postoperative anastomotic leaks in the upper gastrointestinal tract reveal mortality rates in excess of 50 per cent[17,18,28,29]. This may be explained by the fact that intubation of the fistula is impaired by complications resulting from the inevitable leakage around the tube, leading to necrosis of the surrounding tissue by the action of digestive juices, bleeding and recurrent sepsis.

A combination of gastric disconnection and duodenal intubation has been proposed[30]. While this procedure was successful in the absence of adjacent abscesses, it failed in the presence of infection[17].

The rationale of the method presented in this paper is threefold: avoid further dissection, avoid new suture lines and achieve permanent control of the source of infection. A further advantage of continuous irrigation is the prevention of obstruction of drains and ensuring continuous lavage of the area (inside and outside the duodenum), thus continuously neutralizing a source of infection that cannot be exteriorized. Of course this surgical technique is only part of an overall management strategy including prompt diagnosis of postoperative peritonitis, adequate resuscitation, enteral nutrition and dedicated medical care in the setting of a specialized intensive care unit.

Acknowledgements

The authors are indebted to Professor Sir Miles Irving for reviewing the manuscript.

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British Association of Endocrine Surgeons Abstracts

The following abstracts were presented at the British Association of Endocrine Surgeons meeting held in Edinburgh, UK on 27-28 May 1999.

The *British Journal of Surgery* prize was awarded to the abstract entitled 'Investigation of the vasoactive and proliferative effects of parathyroid hormone and parathyroid hormone-related peptide on vascular smooth muscle' by D. R. Chadwick.

Highly selective cervical angiography, venous mapping and selective venous sampling in the localization of parathyroids in re-exploration parathyroid surgery

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Background: Previous neck exploration may result in anomalous venous drainage rendering venous sampling potentially inaccurate. The results of angiography, venous mapping and venous parathyroid hormone (PTH) sampling in patients undergoing repeat cervical exploration for hyperparathyroidism were investigated.
Methods: All patients who underwent angiography and venous sampling for recurrent or residual hyperparathyroidism ($n = 25$) or primary hyperparathyroidism after previous thyroid surgery ($n = 2$) from 1 January 1993 to 16 July 1998 were included in the analysis.
Results: Thirty angiograms and venous sampling procedures were performed in 27 patients; 24 patients had 25 cervical re-explorations. In 23 of the re-explorations, abnormal parathyroid tissue was retrieved. The most recent calcium levels were normal in 20 of the 24 patients. Angiography was 74 per cent sensitive and 61 per cent specific. Venous sampling correctly noted the site in 77 per cent of cases. Interpreted together with venous mapping, the accuracy was 86 per cent. Failures were due to unsuspected residual gland hyperplasia, middle mediastinal gland and cancer (diffuse venous drainage). The other cancer in this series was suspected because of universally high PTH levels.
Conclusion: Selective cervical angiography, venous mapping and venous sampling are accurate methods of establishing the site of pathological parathyroid tissue. Anomalous results may indicate the presence of a parathyroid carcinoma.

Risk factors for and outcome of atherosclerotic disease in patients with primary hyperparathyroidism

A. Bergenfelz, J. Westerdahl, S. Tibblin, P. Lindblom and S. Valdemarsson* (introduced by C. Russell)

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Background: Patients with primary hyperparathyroidism (pHPT) have an increased mortality rate from atherosclerosis which is improved by surgery. It is important, therefore, to identify risk factors for atherosclerotic disease (AS) in these patients.
Methods: A total of 145 consecutive patients with pHPT were investigated; 41 had AS.
Results: Univariate analysis demonstrated that patients with AS were older, had higher levels of triglycerides, blood glucose and serum urate, and a higher frequency of hypertension and signs of compromised renal function. There were no differences in serum levels of either calcium or intact parathyroid hormone between patients with and without AS. Univariate risk factors and sex were included in a stepwise logistic regression analysis. Serum urate concentration was found to be the only independent risk factor (odds ratio 4·5 (95 per cent confidence interval 1·3–15)). After operation renal function improved and serum levels of urate and triglycerides decreased in patients without AS. In patients with AS no significant change occurred.
Conclusion: The presence of AS in patients with pHPT was closely associated with impaired renal function and the metabolic syndrome of an increased serum urate level. Biochemical improvement in renal function and metabolic variables was seen only in patients without overt AS.

Sporadic primary hyperparathyroidism in the young

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Background: Sporadic primary hyperparathyroidism (pHPT) in the young is extremely rare. The exact incidence is unknown and little is known of its characteristics. The aim of this study was to determine whether sporadic pHPT in the young differs from that in adults.
Methods: From 1976 to 1998, 34 patients (17 males and 17 females) aged 9–19 years underwent operation for pHPT.
Results: Twenty-eight patients were symptomatic with renal stones, bone disease (ten patients), pancreatitis (one) and vague non-specific symptoms (seven). Mean serum calcium was 3·04 mmol l^{-1} and mean adenoma weight was 930 mg. Thirty-two of the 34 patients were cured. No patient had vocal cord paralysis and one patient developed temporary hypocalcaemia. There were no long-term complications. Two patients developed recurrent disease over a mean follow-up period of 8·5 years. No patient showed evidence of an inherited disorder.

Conclusion: Sporadic pHPT in the young presents as a more severe disease. Physicians should be aware that pHPT may occur in the young in a non-familial setting and may be responsible for a wide spectrum of symptoms. As in the adult population, pHPT is safely and effectively treated by operation.

Lateral approach in endoscopic parathyroid exploration

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Background: Endoscopic parathyroidectomy is a feasible surgical procedure. A lateral approach in the line of the anterior border of the sternocleidomastoid muscle (SCM) was investigated.
Methods: Thirty patients with sporadic primary hyperparathyroidism (pHPT) without previous neck surgery or a goitre were investigated. Ultrasonography and sestamibi scanning were performed before operation. Rapid intact parathyroid hormone assay was used during surgery. Through a 15-mm transversal skin incision on the anterior border of the SCM, a space was created between the carotid sheath and the lateral portion of the strap muscles and the thyroid lobe. Three trocars were inserted: a 12-mm trocar through the incision and two 2·5-mm trocars above and below the first trocar. Carbon dioxide was insufflated to 8 mmHg. Video-assisted parathyroid exploration was carried out with a 10-mm 0° endoscope. Once the adenoma had been identified and dissected, the trocars were removed. The pedicle was clipped and the adenoma extracted through the 15-mm incision.
Results: Conversion to an open procedure was required in five patients. Of the 31 adenomas (one double adenoma), 28 were identified by endoscopic exploration. Mean weight was 931 mg (range from 100 mg to 5 g). Mean operating time was 79 (range 40–130) min. Morbidity consisted of two superficial haematomas in the SCM. All 30 patients were biochemically cured with a follow-up ranging from 6 to 17 months. Only a cosmetic advantage was demonstrated.
Conclusion: Endoscopic parathyroid exploration by a lateral approach is safe, direct and effective. It could have a role in the surgical management of patients with pHPT.

Sestamibi–technetium isotope scintigraphy in localization of parathyroid tumours

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Introduction: Since 1983, preoperative assessment of patients with proven primary hyperparathyroidism (pHPT) has included isotope subtraction scintigraphy to localize the solitary adenoma to be found in approximately 90 per cent of patients. The usefulness of thallium technetium scans was limited by its inability to localize small tumours reliably[1].
Methods: From 1 January 1993 sestamibi was used for imaging in the hope of improving the sensitivity of the scan for small tumours.
Results: Between 1 January 1993 and 3 November 1998, 140 patients (107 women and 33 men of mean age 58·4 years) with pHPT were scanned and subsequently underwent first-time cervical exploration. Two scans were technically unsatisfactory, 29 revealed no residual focus of activity following subtraction, 108 demonstrated a single 'hot-spot' and in one four foci of activity were noted. At operation, of the 138 patients with technically satisfactory scans, 123 had a solitary tumour (122 adenomas, one carcinoma), 12 had multigland disease, and in three no pathological parathyroid tissue could identified. Overall scan sensitivity for localizing a solitary parathyroid tumour was 82·6 per cent. Of 87 tumours weighing more than 500 mg, 81 (93·1 per cent) were localized accurately by scintigraphy; only 16 of 32 adenomas weighing less than 500 mg were identified. Four tumours were not weighed.
Conclusion: Isotope subtraction scintigraphy continues to localize a high proportion of solitary parathyroid tumours accurately, facilitating unilateral cervical exploration for pHPT. The inability of the scan consistently to identify the site of small (less than 500 mg in weight) adenomas is a limiting factor.

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Long-term results of unilateral exploration of the neck for patients with primary hyperparathyroidism

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Background: Controversy about the best surgical approach to primary hyperparathyroidism (pHPT) prompted a review of targeted unilateral exploration.
Methods: Patients who had surgery for pHPT were recalled for clinical and biochemical assessment.
Results: Between 1980 and 1996, 171 patients underwent surgery for primary hyperparathyroidism. Forty had died and 93 (71 per cent) were available for follow-up. All but two patients had subtraction scans to localize the adenoma. In addition to this, 42 patients (45 per cent) had various combinations of ultrasonography, magnetic resonance imaging and computed tomography to aid the localization. There were eight failed and six false localizations. Unilateral exploration was successful in 74 patients (80 per cent) with a median duration of operation of 33 min. Some 19 patients (20 per cent) required bilateral exploration (failed localization, eight; false localization, six; no localization, two; other, three).

The median duration of long-term follow-up for this study was 7 (range 1–13) years. Six patients (6 per cent) had evidence of biochemical recurrence, four of whom were symptomatic.
Conclusion: Unilateral exploration of the neck for pHPT is associated with recurrence and long-term follow-up may be required to detect and treat these recurrences.

Correlation of parathyroid scanning and anatomy in 261 unselected patients with sporadic primary hyperparathyroidism

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Background: The performance of preoperative parathyroid scanning challenges the paradigm of routine bilateral neck exploration for first-time parathyroidectomy. The aim of this study was to establish the performance of parathyroid scanning with cationic complexes in unselected patients with sporadic primary hyperparathyroidism (pPHT).
Methods: The reports of 261 consecutive patients with sporadic pHPT who had preoperative scintigraphy and were cured after operation were analysed. The technique for parathyroid scanning combined imaging using sestamibi or tetrofosmin and thyroid subtraction. Extensive bilateral neck exploration was performed in every patient to identify all parathyroid glands and to excise any macroscopically enlarged gland.
Results: At operation, 1058 parathyroid glands were identified and 351 abnormal glands were excised (mean(s.d.) weight 1388(150) mg). The scanning results were identical with both tracers. Scintigraphy was considered as clinically contributive (correctly depicting at least one abnormal gland) in 205 patients (79 per cent), but only in 42 (66 per cent) of 64 patients with multiglandular disease ($P < 0{\cdot}001$) and in 32 (57 per cent) of 56 with coexisting thyroid disease ($P < 0{\cdot}001$). False-positive uptake was found in 18 patients (7 per cent). If the unilateral approach had been followed in these 261 patients, unilateral neck exploration would have been performed effectively in 164 patients (63 per cent) if based on scintigraphy, compared with 78 (30 per cent) without peroperative guidance ($P < 0{\cdot}001$). Overall, at least one enlarged parathyroid gland would have been neglected in 28 patients (11 per cent) with a unilateral approach based on scintigraphy, compared with 18 (7 per cent) without preoperative guidance.
Conclusion: If used to guide selective surgical exploration, parathyroid scanning with cationic complexes will significantly increase the number of patients undergoing unilateral neck exploration. This strategy will also lead to neglect of at least one enlarged gland in more than 10 per cent of patients.

Role of apoptosis and apoptotic gene expression in Hashimoto thyroiditis

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Background: In Hashimoto thyroiditis (HT), thyroid cells appear to die by apoptosis, possibly through activation of death signals.
Methods: Spontaneous and cytokine-induced Bcl-X expression on thyroid cells and the effect of cytokines on the level of apoptosis were studied.
Results: *In vivo*, decreased Bcl-X expression was observed within the thyrocyte compartment (thymus-expressed chemokine; TEC) of three samples of HT, compared with TECs in ten specimens of Graves disease (GD) and ten of multinodular goitre (MNG). Intrathyroidal lymphocytes (ITLs) were consistently Bcl-X positive. Proinflammatory cytokines decreased Bcl-X expression on thyrocytes and increased apoptosis. TECs in HT contributed substantially to the level of apoptosis, which was increased by ITL removal (from 49 to 74 per cent). Following the suggestion that thyrocytes in HT can kill one another through Fas–Fas ligand interaction, the ability of thyroid cells to kill Fas-expressing targets was studied in one GD, one MNG and three HT glands. The ability was confirmed. Both TEC- and ITL-enriched preparations from GD were effective at killing heterologous and autologous Fas-expressing targets. Conversely, ITLs but not TECs from a HT gland could exert limited killing. Fas-dependent killing could not be prevented by Fas ligand or Fas receptor blocking monoclonal antibodies. However, trypsin was effective and VAD-FMK caspase inhibitor showed a small but consistent inhibition of killing.
Conclusion: These findings suggest that in HT, TECs are poorly functional. Their death may be the result of 'neglect' due to impairment of regulatory antiapoptotic genes. The activation of a death signal could also play a role, although the interactions of apoptotic receptor pairs different from Fas–Fas ligand may be involved.

Phaeochromocytoma associated with phacomatosis

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Background: Phacomatoses described in association with phaeochromocytoma include von Hippel–Lindau (VHL) disease, neurofibromatosis type 1 (NF-1), Sturge–Weber syndrome and tuberous sclerosis.
Methods: The charts of all patients operated on for a phaeochromocytoma from 1970 to 1998 were reviewed to determine those associated with phacomatosis.

Results: There were 174 patients with phaeochromocytoma; 15 (8·6 per cent) had an association to either VHL disease or NF-1. No association was observed with other types of phacomatosis. Eight patients (4·6 per cent) had associated VHL disease and seven (4·0 per cent) had associated NF-1. Age ranged from 14 to 59 (median 35·5) years. Thirteen patients presented with hypertension, 15 had intra-adrenal lesions, five were bilateral and 15 were benign. In four patients the phaeochromocytoma was the first manifestation of the disease. Follow-up ranged from 6 months to 16 years. No patient developed a contralateral intra-adrenal phaeochromocytoma after unilateral adrenalectomy. One patient died from an unassociated cause.

Conclusion: Phaeochromocytoma was associated with two types of phacomatosis, VHL disease and NF-1, with a frequency of 4·6 and 4·0 per cent respectively. All had intra-adrenal lesions.

Morbidity of open adrenalectomy for phaeochromocytoma in patients now considered suitable for laparoscopic excision

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Background: Laparoscopic excision of phaeochromocytoma is becoming accepted as the treatment of choice since Gagner *et al.*[1] demonstrated that the procedure is not contraindicated. However, a knowledge of morbidity and mortality associated with the open approach is required for audit before there is universal acceptance of the laparoscopic approach.

Methods: The notes of all patients who had undergone excision of phaeochromocytoma in the 10 years to 1998 were retrieved and searched. Patients were excluded from the study if they would not have undergone laparoscopic excision by current criteria.

Results: A total of 41 patients underwent excision of phaeochromocytoma. Of these, 31 would currently have undergone laparoscopic excision. Four patients were excluded for malignant tumours and six due to size. The overall morbidity rate was 71 per cent. The most common complication was chest infection, which required antibiotics in 43 per cent of patients. Cardiac complications occurred in three patients. Other complications included haemorrhage, wound haematoma and incisional hernia. One death occurred due to postoperative pulmonary embolus.

Conclusion: The morbidity rate for open excision of phaeochromocytoma is high, although the mortality rate is low (one of 41 patients). These figures imply that there may be scope for improvement, but it is not known whether laparoscopic excision will achieve this.

Reference

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Investigation of the vasoactive and proliferative effects of parathyroid hormone and parathyroid hormone-related peptide on vascular smooth muscle

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Background: Hyperparathyroidism (HPT) is associated with an increased incidence of hypertension and cardiovascular disease. The contraction and proliferation of rat vascular smooth muscle cells (VSMCs) in response to vasoconstrictors is increased by previous prolonged exposure *in vitro* to parathyroid hormone (PTH), due to desensitization of the normally inhibitory effects of PTH-related peptide (PTHrP). The effects of PTH and PTHrP on contraction and proliferation of human vascular smooth muscle were studied to establish whether or not desensitization occurs in patients with HPT.

Methods: (1) Isometric tension *in vitro* was measured in segments of superior thyroid artery and anterior jugular vein obtained at neck surgery in normotensive patients with HPT ($n = 6$) and a eucalcaemic control group undergoing thyroid surgery ($n = 12$). Vessels were contracted with noradrenaline to allow the vasodilatory effects of PTH and PTHrP to be observed. (2) Human VSMCs were cultured in 0·5, 5 and 15 per cent serum with or without PTH (10^{-11} to 10^{-7} mol l^{-1}) and proliferation was assessed by cell counts after 14 days.

Results: (1) Vasodilatation in response to PTH or PTHrP (up to 100 nmol l^{-1}) was not observed with venous segments ($P > 0\cdot36$, Wilcoxon signed-rank test for paired data). However, both PTH 20 nmol l^{-1} and PTHrP 100 nmol l^{-1} dilated precontracted arterial segments. The degree of vasodilatation produced was similar in the control and HPT groups ($P > 0\cdot08$, Mann–Whitney U test) (see *Table*).

Table Percentage of arterial vasodilatation produced

	Controls	HPT
PTH 20 nmol l^{-1}	55 (37–72)	36 (1–50)
PTHrP 100 nmol l^{-1}	39 (25–64)	39 (17–56)

Values are median (95 per cent confidence intervals)

Preincubation of control arteries with PTH 50 nmol l^{-1} for 1 h did not influence subsequent vasodilatory responses to PTHrP 100 nmol l^{-1} ($P = 0\cdot89$, Wilcoxon test). (2) No effects of PTH on serum-induced proliferation of venous or arterial VSMCs were observed.

Conclusion: These data do not support the hypothesis that homologous desensitization to PTH or PTHrP is implicated in the pathogenesis of vascular disease in HPT.

Genotype–phenotype correlations in hereditary medullary thyroid carcinoma

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Background: In hereditary medullary thyroid carcinoma (MTC), genotype–phenotype correlations have not yet been established.

Methods: Germline mutations in exons 10, 11, 13 and 14 were identified in 42 (31 per cent) of 136 patients operated on for MTC between May 1995 and November 1998. Exon mutations in these patients were correlated with age at diagnosis, sex, pathological tumour node metastasis (pTNM) category, Union Internacional Contra la Cancrum stage, number of involved lymph nodes and biochemical cure.

Results: Mutations in exons 10, 11, 13 and 14 were demonstrated in ten (24 per cent), 24 (57 per cent), six (14 per cent) and two (5 per cent) of the 42 patients. These patients differed significantly in their mean(s.d.) age at diagnosis: 35(15), 31(16), 55(16) and 62(2) years respectively ($r = 0{\cdot}32$, $P = 0{\cdot}01$). When patients were grouped by amino acid exchange in cysteine domains (exons 10 and 11 *versus* 13 and 14) the difference was even greater: 32(16) *versus* 57(14) years ($r = 0{\cdot}52$, $P = 0{\cdot}001$). No other significant associations were noted.

Conclusion: Only age at diagnosis was found to reflect tumour biology. The cysteine domains of exons 10 and 11 clearly account for rapid malignant transformation.

Individual timing of prophylactic surgery in multiple endocrine neoplasia type II gene carriers according to mutated codon

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Background: The identification of different *RET* germline mutations should help optimize the timing of prophylactic surgery in proven multiple endocrine neoplasia type II (MEN-II) gene carriers.

Methods: A pan-European survey was conducted by questionnaire. Inclusion criteria were proven *RET* germline mutation, lack of clinical symptoms, age less than 20 years, and pT_{0-1}, $pN_{x/0-1}$, M_0. For each mutated codon, the earliest age at presentation was recorded for both C-cell hyperplasia (CCH) and medullary thyroid carcinoma (MTC).

Results: To date, 139 patients with CCH or MTC have been enrolled. Based on patient age of earliest manifestation, three separate risk groups were devised: the high-risk group (codons 634 and 618) revealed CCH at age 1 year, and MTC at ages 1 and 7 years. The intermediate risk group (codons 620, 790 and 891) showed CCH at ages 3 and 5 years, and MTC at ages 11 and 13 years. The low-risk group (codons 611, 623, 768, 791 and 804) exhibited CCH at ages 8, 9, 15, 10 and 7 years, and MTC at age 21 years (codon 611), whereas the remaining codons (623, 768, 791 and 804) were unaffected by MTC before the age of 20 years.

Conclusion: Prophylactic surgery should be scheduled before the age of 6, 10 and 20 years in groups at high, intermediate and low risk respectively.

Mapping of a gene predisposing to familial thyroid tumours with cell oxyphilia to chromosome 19

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Background: Familial non-medullary thyroid carcinoma (FNMTC) is a clinical entity characterized by a more aggressive phenotype than the sporadic counterpart. Families with recurrence of NMTC have been reported repeatedly in the literature, and epidemiological data show a very high relative risk for first-degree relatives of probands with thyroid cancer. The transmission of susceptibility to FNMTC is compatible with autosomal dominant inheritance with reduced penetrance or with complex inheritance. Cases of benign thyroid disease are often found in FNMTC kindreds. The identification of a new entity of FNMTC and the mapping of the responsible gene named *TCO* (for thyroid tumour with cell oxyphilia) are reported.

Methods: In one family, six individuals were diagnosed at first with multinodular goitres and three with papillary thyroid carcinoma. Eight patients were operated on. Full clinical and pathological information was obtained. Pathological findings were available in five cases. No patient had a history of radiation exposure. Blood samples were collected from the nine affected patients and from eight unaffected relatives after obtaining their informed consent. The gene was mapped by linkage analysis with a whole-genome panel of microsatellite markers.

Results: Pathology showed multiple, well demarcated tumours composed of follicular structures, papillae, solid trabecular areas or an admixture of these. The neoplastic cells from all lesions showed characteristic faint to marked cytoplasmic oxyphilia. All tumours showed thyroglobulin immunoreactivity and were negative for calcitonin. A random genome screen was undertaken, and after genotyping a total of 226 microsatellites, covering approximately 75 per cent of the genome, a LOD score of 2·41 at $\theta = 0$ for marker D19S586 was found. Additional markers were typed in the region and were found to be in linkage, with LOD scores peaking at markers D19S916 ($Z_{max} = 3{\cdot}01$ at $\theta = 0$) and D19S413 ($Z_{max} = 2{\cdot}95$ at $\theta = 0$). All the above markers have been physically mapped to 19p13.2.

Conclusion: *TCO* was mapped to chromosome 19p13.2 by linkage analysis with a whole genome panel of microsatellite markers. Interestingly, both the benign and malignant thyroid tumours in this family exhibited some extent of cell oxyphilia, which has not been described until now in the familial forms of NMTC. These findings suggest the need to investigate carefully the relatives of patients affected with sporadic NMTC with cell oxyphilia.

Utility of frozen-section histology in the surgical management of thyroid nodular disease

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Background: Thyroid nodules are the commonest disorder presenting to the thyroid surgeon. The majority of such lesions are benign but the principal problem facing the clinician is that of identifying the malignant nodule requiring surgery. Selection for surgery is based primarily on a combination of clinical assessment and fine-needle aspiration cytology (FNAC). Frozen-section (FS) histology has traditionally been employed as an integral part of the operative strategy to confirm the preoperative diagnosis and also to influence to the extent of surgical resection.
Methods: The utility of FS histology was reviewed in a series of 155 patients undergoing surgery for nodular thyroid disease, each patient having preoperative FNAC, intraoperative FS histology and postoperative definitive paraffin-section histology.
Results:

Table Comparative analysis of FS histology based on FNAC categories

	Malignant	Benign	Suspicious	Inadequate
Sensitivity (%)	100	62	64	75
Specificity (%)	—	98	98	95
Accuracy (%)	100	93	92	92
PPV (%)	100	83	88	75
NPV (%)	—	94	92	95

PPV, positive predictive value; NPV, negative predictive value

Conclusion: When the FNAC findings show malignancy, FS histology is unnecessary and contributes little to management. FS histology may be of value when FNAC indicates the lesion is benign, suspicious or inadequate, permitting identification of some malignant lesions that would otherwise require a second operation in order to complete a total thyroidectomy.

Sex and clinical findings predict outcome in 1005 patients investigated by fine-needle aspiration cytology for thyroid enlargement

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Background: An audit of the value of fine-needle aspiration cytology (FNAC) in the diagnosis of thyroid malignancy was undertaken.
Methods: A total of 1005 euthyroid patients who presented with thyroid enlargement were evaluated by FNAC of the thyroid as the first-line investigation. The cohort comprised 870 women and 135 men (mean age 47 years), and thyrotrophin (thyroid-stimulating hormone; TSH) concentration was measured by a sensitive assay in 500 subjects.
Results: Some 312 patients proceeded to surgery, including those with suspicious (168 patients) or malignant (23) cytology, upper airway obstruction (44), recurrent cysts (six), persistent non-diagnostic cytology (four) and cosmetic reasons (67). Those not treated surgically were followed for a minimum of 2 (range 2–14; mean 6·7) years. The overall sensitivity and specificity of the procedure in the detection of thyroid neoplasia were 88 and 89 per cent respectively. Men who presented with thyroid enlargement had significantly higher rates of malignancy ($P = 0{\cdot}007$) and neoplasia ($P = 0{\cdot}002$) than women, as did patients with solitary nodules compared with those with diffuse or multinodular goitres (malignancy $P = 0{\cdot}001$; neoplasia $P < 0{\cdot}001$). Patients with normal TSH levels (greater than 0·4 m units l^{-1}) at presentation had a non-significantly increased risk of thyroid neoplasia ($P = 0{\cdot}07$) and malignancy, in contrast to those with a low TSH concentration (less than 0·4 m units l^{-1}).
Conclusion: FNAC of the thyroid is an accurate test in the diagnosis of thyroid neoplasia. Gender and goitre type at presentation both contribute significantly to the prediction of risk of underlying thyroid neoplasia.

Place of total thyroidectomy for benign thyroid disease

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Background: Total thyroidectomy eliminates the possibility of recurrent goitre and hyperthyroidism when carried out for benign disease. However, such a radical approach remains controversial because of the potential for increased morbidity associated with injury to the recurrent laryngeal nerves (RLNs) and parathyroid glands. This study reviewed the results of total thyroidectomy in patients with benign thyroid disease.
Methods: Between 1988 and 1998, 172 patients (150 women and 22 men of mean age 53 years) underwent total thyroidectomy for multinodular goitre (MNG) ($n = 152$) or Graves' disease ($n = 20$).

Results: There were no perioperative deaths. Mean weight of resected thyroid was 178 g (189 g for MNG; 86 g for Graves' disease). Permanent unilateral vocal cord paralysis occurred in three patients, representing injury to 0·9 per cent of RLNs at risk. In addition nine individuals sustained temporary unilateral vocal cord paralysis (2·6 per cent of RLNs at risk). Symptomatic hypocalcaemia occurred in 55 patients (31·9 per cent). The incidence of hypocalcaemia was higher in patients with Graves' disease (ten of 20) than in those with MNG (45 (29·6 per cent) of 152)) but the difference was not statistically significant. At completion of review on 31 July 1998, nine patients (5·2 per cent) remained on calcium supplements. Of these, six had surgery for MNG and three for Graves' disease ($P = 0{\cdot}07$, Fisher's exact test).

Conclusion: Total thyroidectomy for multinodular goitre can be performed safely with acceptable morbidity. The increased incidence of symptomatic hypocalcaemia after total thyroidectomy for Graves' disease represents a cause for concern.

Recurrent multinodular goitre

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Background: There has recently been some debate in the literature as to whether total or subtotal thyroidectomy should be the treatment of choice for benign colloid goitre. The current debate has placed emphasis on the comparison of complication rates in the short term, but has failed to address the important difference in recurrence rates between the two operative techniques.

Methods: A retrospective case-note study was carried out at Manchester Royal Infirmary and North Manchester General Hospital which identified 66 patients (39 : 27 in the respective hospitals) who had subtotal thyroidectomy between 5 and 13 years ago for benign multinodular goitre. The diagnosis was made if it was stated in the discharge letter or on the pathology form. A total of 37 patients replied to a postal questionnaire. All the remaining patients were telephoned, if possible, as well as those who had not filled in the form correctly.

Results: A total of 42 patients (64 per cent) were successfully contacted and assessed for the presence of any recurrent goitre or symptoms. Eleven patients were found to have a recurrent goitre on clinical examination by a consultant endocrine surgeon or on ultrasonography. The remaining 31 patients were either symptom-free or had no objective clinical evidence of goitre.

Conclusion: This study shows that over 5–13 years following subtotal thyroidectomy for benign multinodular goitre there was clinical recurrence of goitre in 11 (26 per cent) of 42 patients.

Prospective cohort study of early prediction of outcome of hypocalcaemia after thyroidectomy

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Background: Permanent hypoparathyroidism (PHP) may lead to malpractice litigation. This prospective study was designed to assess the clinical relevance of potentially predictive criteria for the outcome of hypocalcaemia after thyroidectomy.

Methods: From January 1994 to December 1997, serum calcium and phosphorus levels were measured in 2035 consecutive patients undergoing bilateral thyroidectomy. Patients with postoperative hypocalcaemia (calcium levels lower than 2 mmol l^{-1} on 2 consecutive days) were included in the study. Parathyroid hormone (PTH) concentration was determined before the initiation of calcium therapy (early PTH level). All patients were then followed until complete resolution of hypocalcaemia. Those needing substitutive therapy to maintain normocalcaemia 1 year after surgery were considered to have PHP. Correlation of outcome with clinical characteristics, postoperative and delayed (7–14 days after discharge) calcium and phosphorus levels, and early PTH level, were examined statistically.

Results: Postoperative hypocalcaemia occurred in 153 patients (7·5 per cent) and recovered spontaneously in all but seven patients (0·3 per cent). Early PTH, delayed calcium and phosphorus levels were found to be predictive for outcome of hypocalcaemia by univariate analysis ($P < 0{\cdot}01$). Both delayed calcium and phosphorus levels appeared as independent factors ($P < 0{\cdot}001$) on multivariate logistic regression analysis.

Conclusion: Delayed serum calcium and phosphorus levels accurately predict the outcome of patients with hypocalcaemia after thyroidectomy. When delayed calcium concentration is less than 2 mmol l^{-1} and/or delayed phosphorus concentration is greater than 0·4 mmol l^{-1}, long-term follow-up should be strictly enforced to detect PHP.

Audit of hypocalcaemia after thyroid surgery

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Background: Hypocalcaemia after thyroidectomy is common and mostly transient, but, if permanent, long-term replacement therapy is required. The importance of informing patients of rates of permanent hypoparathyroidism has recently been emphasized[1]. This study audited hypocalcaemia after bilateral thyroid surgery.

Methods: A retrospective note study of patients undergoing total or subtotal thyroidectomy between March 1995 and August 1998 was undertaken.

Results: Some 92 patients (78 female; mean age 50 (range 8–83) years) were identified. Seventy underwent total thyroidectomy, of which 17 operations were for malignancy. Fifteen patients underwent operation for thyrotoxicosis. After thyroidectomy, hypocalcaemic symptoms were documented in 27 patients, of whom 20 (22 per cent) had calcium levels below

2 mmol l^{-1} on one occasion. In ten patients hypocalcaemia remained below 2 mmol l^{-1} for 2 days. At 6 months after operation eight patients (9 per cent) had persistent hypocalcaemia. All had undergone total thyroidectomy, four for malignancy and four for symptomatic multinodular goitre. Permanent hypocalcaemia occurred significantly more frequently after operation for malignant disease ($P = 0{\cdot}04$).

Conclusion: This audit revealed a high rate of hypoparathyroidism, particularly after total thyroidectomy for neoplasia. If local data are to be revealed during informed consent, such an audit will provide the appropriate information.

Reference

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Altered parathyroid calcium sensitivity and/or change in peripheral calcium metabolism in early hypocalcaemia after hemithyroidectomy

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Background: Thyroid operations are frequently complicated by postoperative hypocalcaemia. Although damage to the parathyroid glands probably plays an important role, the pathophysiology remains obscure.

Methods: Eight patients who underwent hemithyroidectomy for benign thyroid disease were investigated. All patients had normal serum levels of calcium and thyroid hormones before operation. The function of the parathyroid glands was studied with a 60-min ethylenediamine tetra-acetic acid (EDTA) infusion test before operation and on postoperative days 1, 7 and 30. Serum levels of ionized calcium and of parathyroid hormone (PTH) were determined every 10 min.

Results: Serum levels of ionized calcium decreased on the first postoperative day (1·16 *versus* 1·24 mmol l^{-1} before operation; $P < 0{\cdot}01$). During the EDTA infusion test the serum levels of PTH at 60 min and the area under the curve (AUC) for PTH were slightly decreased ($P < 0{\cdot}05$). At 7 days after operation serum levels of ionized calcium were still decreased ($P < 0{\cdot}05$), whereas basal serum PTH levels were unchanged ($P = 0{\cdot}17$). Similarly, during the EDTA infusion test serum levels of PTH at 60 min as well as the AUC for PTH during the test were unchanged ($P = 0{\cdot}92$ and $P = 0{\cdot}17$ respectively). At 30 days after operation, serum levels of ionized calcium and PTH were normalized.

Conclusion: The results of this investigation suggest that low levels of calcium after hemithyroidectomy are partly due to a decrease in parathyroid calcium sensitivity and/or a change in peripheral calcium metabolism.

Effect of total thyroidectomy on exophthalmos in Graves' disease

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Background: Previous reports have indicated that surgical treatment for Graves' disease could have beneficial effects on thyroid eye disease. To investigate further the role of thyroidectomy on exophthalmos, a prospective study was undertaken.

Methods: All patients with Graves' disease were submitted to total thyroidectomy irrespective of the presence of overt exophthalmos at the time of operation. They all underwent orbital computed tomography (CT) before, and at 3, 6 and 12 months after, operation. The level of the CT section was the same for all patients at all stages (alongside the optic nerve of both eyes). On each CT scan three dimensions were measured: (a) back of eyeball to orbital bone; (b) front of eyeball to orbital bone; and (c) transverse orbital.

Results: Between January 1992 and July 1993, 49 patients were recruited; at completion of the study there were 36 patients (11 men and 25 women of mean age 42·3 years), of whom 12 had clinically overt exophthalmos at the time of operation (group 1) and 24 (group 2) had no symptoms or signs. Dimensions (a) and (b) decreased significantly between the period before and 12 months after operation in both exophthalmic (group 1; $P = 0{\cdot}027$ and $P = 0{\cdot}02$ respectively) and non-exopthalmic (group 2; $P = 0{\cdot}04$ and $P = 0{\cdot}0033$) patients, while dimension (c) increased significantly during the same period in both groups ($P = 0{\cdot}0077$ and $P = 0{\cdot}05$). By calculating the area around the eye, based on dimensions (a) and (c), it was demonstrated that 1 year after operation this area showed a significant decrease in group 2 but not in group 1 ($P = 0{\cdot}035$, Wilcoxon test).

Conclusion: Total thyroidectomy may be effective in ameliorating exophthalmos, whether clinically overt or not. Orbital CT can be used as an objective technique for measuring exophthalmic changes.

Graves' disease and thyroid nodules

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Background: The aim of this multicentre study was to review patients operated on for Graves' disease associated with thyroid nodules to evaluate the risk of associated thyroid carcinoma.

Methods: A total of 557 consecutive patients operated on for Graves' disease between 1991 and 1997 in five endocrine surgery departments were reviewed retrospectively. Each patient underwent clinical, biochemical, ultrasonographic and scintigraphic evaluation. No patient had a previous history

of radioactive iodine therapy or external irradiation. Surgery consisted of either subtotal or total thyroidectomy.
Results: Cold nodules were observed in 140 patients (25·1 per cent) (16 women, 124 men) with mean age of 42 (range 11–74) years. Thyroid carcinoma was diagnosed in 21 (15·0 per cent), always inside a nodule. The incidence of thyroid carcinoma associated with Graves' disease was 3·8 per cent (21 of 557 patients). Histological examination revealed 20 papillary and one follicular carcinomas. Tumour diameter ranged from 2 to 25 mm and the nodule was palpable in eight patients. Carcinoma was multifocal in ten patients.
Conclusion: This multicentre study showed a 3·8 per cent rate of carcinoma in patients with Graves' disease and a 15·0 per cent rate in those with Graves' disease associated with cold nodules.

Surgical management of hyperparathyroidism

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Background: The indications for and extension of thyroidectomy in the management of hyperthyroidism are controversial.
Methods: A total of 147 patients with hyperparathyroidism underwent surgical treatment between 1992 and 1997. Two-thirds of the patients were women. Ninety-five patients had toxic multinodular goitre, 39 had Graves' disease and 13 had a toxic solitary adenoma.
Results: Of 134 patients with bilateral disease, near-total thyroidectomy (NTT) was performed in 96 and bilateral subtotal thyroidectomy (BSTT) in 38. There were no differences in the complication rates between the two procedures. The cumulative temporary rate for recurrent nerve paresis and hypocalcaemia was 9 and 14 per cent respectively. Only one patient had recurrence at 2 years after BSTT.
Conclusion: In this study NTT provided good control of hyperthyroidism, although there was a relatively high rate of complications.

An evolving practice in surgery for Graves' disease

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Background: The various treatment options for Graves' disease are implemented in a variety of ways, both geographically and over time. Some 10 years ago the authors reported the outcome of surgery in a cohort of 161 patients with Graves' disease in north-east Scotland treated between 1976 and 1985 (16 per annum) and made a number of recommendations on patient management. During 1986–1997, 100 patients (eight per annum) underwent operation for Graves' disease, which represents a 50 per cent reduction in the number of operations despite an apparently stable incidence of the disease.
Methods: Twenty-three patients had a total or near-total thyroidectomy and commenced thyroxine replacement therapy immediately after operation. Ten women who were either pregnant at the time or intended to become pregnant shortly afterwards were also commenced on T4 immediately after operation, although in two this was subsequently withdrawn.
Results: Of the 69 patients undergoing subtotal thyroidectomy with a view to preserving function, 79 per cent were euthyroid at 1 year. A relationship between remnant weight and thyroid failure at 1 year was again observed. Thyroid failure continued to develop over the study period. Recurrent thyrotoxicosis developed in four patients with a mean follow-up of 6·4 years.
Conclusion: The reduced number of operations for Graves' disease reflects increased use of radioiodine, and the changes in operative technique suggested 10 years ago have resulted in a reduction in recurrent toxicity (8 *versus* 4 per cent at 5 years). The incidence of thyroid failure has increased as consequence of increased use of surgical thyroid ablation in selected patients.

Surgical γ probe for detection of lymph node metastases in patients with differentiated thyroid cancer

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Background: In patients with differentiated thyroid cancer, lymph node metastases are frequent at surgery and/or at the first scan with iodine-131. Lymph node metastases can be cured with one or two treatments with iodine-131 (100 mCi). In some patients, persistence of lymph node metastases will be found after several treatments.
Methods: To reduce patient irradiation and to achieve a definitive surgical approach, a surgical γ probe (C-Trak-Sorin; Biomedica, Italy) was used in this study. Six patients with persistence of local tumour or cervical lymph node metastases from papillary thyroid cancer were studied. They were treated with a high dose of iodine-131 followed (7 days later) by surgery using the γ probe. Measurements of radioiodine uptake at the site of metastases, in the blood and during surgical operation were made.
Results: The presence of iodine-131 activity in cervical lymph nodes was evident in five patients, and in one patient activity was demonstrated in the right thyroid bed. A significant difference was shown between the background radioactivity and the site of metastasis in all patients but one. During operation the γ probe revealed the radioactivity and allowed removal of tumour. After operation all neoplastic lesions were controlled using a γ camera with a high-energy collimator, and were confirmed as neoplastic by histological examination. After 48–72 h all patients were scanned and this confirmed the disappearance of radioactivity at the site of metastases.
Conclusion: This study demonstrates the value of the γ probe in allowing radical excision of neoplastic lesions marked by previous administration of iodine-131.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing.

Experimental study of the effect of intraperitoneal heparin on tumour implantation following laparoscopy

Sir

We read with interest the article by Neuhaus *et al.* (*Br J Surg* 1999; **86**: 400–4) in which the authors show that heparin may reduce tumour cell implantation. As well as directly decreasing tumour cell adherence, there are numerous other ways in which heparin may act, including inhibition of the formation of thrombin, which has a role in enhancing tumour growth and metastasis. Thrombin may play a role in the activation of progelatinase A[1], of which the active form, matrix metalloproteinase 2, is thought to play an important role in angiogenesis[2] and tumour invasion[3]. Thrombin may also have a direct proangiogenic effect by inducing differentiation of endothelial cells into capillary structures[4].

The effects of thrombin may also, therefore, be inhibited by the use of intraperitoneal heparin during laparoscopic surgery and decrease the incidence of abdominal wall metastases as observed in this department[5].

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1 Zucker S, Mirza H, Conner CE, Lorenz AF, Drews M, Bahou WF *et al.* VEGF induces tissue factor and matrix metalloproteinase production in endothelial cells. conversion of prothrombin to thrombin results in progelatinase A activation and cell proliferation. *Int J Cancer* 1998; **75**: 780–6.
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Effect of training on the incidence of nerve damage in thyroid surgery

Sir

I read with interest the article by Lamadé *et al.* (*Br J Surg* 1999; **86**: 388–91) which highlights important aspects of surgery and surgical training.

I compliment the authors for carrying out this study. In a changing world with periods of surgical training shrinking (particularly in the UK) and the ever-increasing climate of litigation and compensation, both the trainers and the trainees find themselves under considerable duress. Articles such as this and others[1–3] facilitate surgical training and encourage trainers to overcome long-held views as to what a trainee can safely perform under supervision without compromising patient safety and eventual outcome.

It would have been interesting to know the time taken for similar procedures by the three groups as the time factor is the often-quoted constraint that denies possible surgical opportunities to the trainee.

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Current management of acute leg ischaemia: results of an audit by the Vascular Surgical Society of Great Britain and Ireland

Sir

We read with interest the article by Campbell *et al.* (*Br J Surg* 1998; **85**: 1498–1503) and appreciate the work done by the Vascular Society of Great Britain and Ireland. We do not have such data in our country and the use of trials creates valuable effects in our practice. We would appreciate clarification of two issues.

First, the delay period mentioned in *Table 4* is very important. The extent of the delay is critical in deciding any intervention or surgery for limb salvage. Does the mortality of the procedure have a correlation with the delay period. No data are given on the delay period.

Second, the terms 'dubious', 'viable' and 'non-viable' (*Tables 6* and *7*) need further explanation in the understanding of the type of ischaemia. The further comments of Campbell *et al.* will help us to understand the pitfalls of limb-salvage surgery.

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Author's reply

Sir

We thank Dr Akgun and colleagues for their interest in our paper. Their questions expose the acknowledged limitations of this kind of survey. It did not seem reasonable to analyse the data on delay in presentation for two reasons. First, our definition of acute ischaemia left the time of onset uncertain. Case selection was left to the judgement of individual surgeons and included patients with a sudden deterioration in blood supply up to 2 weeks before presentation. This meant that we did not know how long the acute ischaemia had been present before the patient presented. Second, whether or not any delay had occurred was also left to the subjective judgement of those involved. Any analysis of outcome in the context of perceived delay would, therefore, have been most suspect, and we did not feel that this was fair or scientifically proper.

The terms 'viable', 'dubious' and 'non-viable' were used simply as the best way of allowing surgeons to make a global judgement on the state of the limb. We recognized that, in addition to limbs that were definitely viable and definitely not viable, there were likely to be some that were still in a critical state and that might well be lost shortly after the end of the 30-day observation period. As with the perception of 'delay', these were subjective judgements designed to accommodate a miscellany of patients and surgeons in a large study involving nearly 200 hospitals.

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Leucocyte count and C-reactive protein in the diagnosis of acute appendicitis

Sir

I read with interest the paper by Grönroos and Gronroos (*Br J Surg* 1999; **86**: 501–4). Any effort to reduce the incidence of unnecessary appendectomy is to be commended. However, I feel the use of C-reactive protein (CRP) in the diagnosis of acute appendicitis cannot be justified with the given data. If one looks at the overall numbers presented, only one-quarter of the patients operated on, with an uninflamed appendix, would have been saved an operation if CRP levels had been taken into account. Of the patients studied, this represents only 7–8 per cent and most were women. It is these patients in whom there should be a high clinical suspicion of other diagnoses. They would be suitable for diagnostic laparoscopy to help make definitive diagnosis[1].

The decision to operate or to observe is often made soon after admission and on clinical grounds alone. Given the prolonged turnaround time for what are considered non-urgent laboratory tests in an average hospital the decision to operate would be delayed to at least the next day.

In conclusion, the addition of CRP to the diagnostic decision making in patients who may have acute appendicitis is currently impractical in British clinical practice. The current trend towards laparoscopy in women with right iliac fossa pain makes the measurement of CRP obsolete.

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1 Laine S, Rantala A, Gullichsen R, Ovaska J. Laparoscopic appendectomy – is it worthwhile? A prospective, randomized study in young women. *Surg Endosc* 1997; **11**: 95–7.

Author's reply

Sir

I thank Dr Taylor for his comments but disagree, and the difference between our views may be due to the fact that in Finland the measurement of CRP is a laboratory test which is easily performed and available at all times in hospitals with a surgical unit. I understand this is not the case in the UK.

I trust measuring CRP level is worthwhile in excluding acute appendicitis. One-quarter of the negative appendectomies can be avoided if both leucocyte count and CRP are not elevated and I believe that laparoscopy is unnecessary in this situation. If clinical symptoms and signs continue and leucocyte count and/or CRP value increases above the upper limit of the reference interval, the patient should undergo laparoscopy to establish a precise diagnosis. Otherwise, careful clinical follow-up should be continued and additional blood samples should be taken for leucocyte count and CRP measurements. We have changed our own treatment strategy accordingly and experience so far is encouraging.

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Interstitial laser coagulation for hepatic tumours

Sir

The excellent review of interstitial laser coagulation (ILC) by Heisterkamp *et al.* (*Br J Surg* 1999; **86**: 293–304) offered a comprehensive insight into potential applications of this modality for irresectable liver tumours. However, we feel that there are unanswered questions.

The major limitation of laser coagulation is the small lesion size generated by this technique[1,2]. The authors indicated that increasing the power would result in an increase in the area of coagulation, but with an increase in power there will be an increase in resistance and a reduction in heat conductance due to charring effects leading to a reduced lesion size[3]. The characteristics of the tumour are crucial factors. We have found that laser ablation was ineffective for patients with tumours with a high fibrous component such as cholangiocarcinoma (unpublished material). Heat is lost from tissue during laser coagulation via conduction and low-resistance shunting[4,5]. Thus, to achieve effective tumour coagulation some additional methods should be available when treating perivascular lesions[5]. Although the immediate effect of laser coagulation on tumour tissue can be revealed clearly by ultrasonography following tissue heating, the appearance of tumours changed very little after ILC because of the charcoal effect. This could make postoperative interpretation of the effectiveness of the treatment misleading. Visceral angiography may be valuable[5].

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Author's reply

Sir

The valuable comments of Messrs Jiao and Habib allow us to emphasize the aspects of interstitial laser coagulation (ILC) essential for the destruction of large volumes of tissue. Resistance of the tissue, pivotal in radiofrequency coagulation, does not cause the carbonization found with conventional laser fibres in ILC. Charring is the result of concentrated light emission at the tip with further absorption of light by the blackened tissue and preventing further light emission into the tissue. The argument that the characteristics of the tumour are crucial is not supported by evidence in the literature. The advantage of ILC is the induction of symmetrical and reproducible coagulation which makes the technique particularly suitable for solid intraparenchymal tumours. The lack of success in the patient with cholangiocarcinoma might be related to the diffuse spreading pattern of the tumour rather than the high fibrous content. As stated in the review ultrasonography has no place in real-time monitoring of ILC as the echogenic area does not correlate with the coagulative damage. This is not because of charring but because the formation of gas bubbles results in a heterogeneous image.

We emphasized that the use of a cylindrical light-diffusing tip in an internally water-cooled sheet (combined with hepatic vascular inflow occlusion during laser treatment) results in coagulated volumes of 5 cm diameter. We hypothesize that this combination leads to a higher percentage of successful treatments in a single session when compared with the results of current application of ILC for colorectal metastases and percutaneous ethanol injection for hepatocellular carcinoma. In an ongoing study the safety, feasibility and initial response rate of percutaneous ILC with vascular inflow occlusion is being assessed in patients with irresectable colorectal metastases or hepatocellular carcinoma (largest diameter 4 cm). Triphasic contrast-enhanced spiral computed tomography is used to evaluate tumour response[1]. In nine patients, 11 laser treatments have been performed for 13 tumours. Minor complications were noted in five treatments, but complete coagulation at 24 h was 70 per cent with no failures in the last seven treated tumours. These results encourage us to determine the duration of response in a larger group of patients.

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1 Amin Z, Donald JJ, Masters A, Kant R, Steger AC, Bown SG *et al.* Hepatic metastases: interstitial laser photocoagulation with real-time US monitoring and dynamic CT evaluation of treatment. *Radiology* 1993; **187**: 339–47

Risk scoring in surgical patients

Sir

We read with interest the review by Jones and de Cossart (*Br J Surg* 1999; **86**: 149–57) who concluded that the Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) is the most appropriate scoring system for the general surgical population while briefly mentioning the Portsmouth modification of POSSUM (P-POSSUM) as an alternative scoring system. They stated that if an exponential analysis was used[2], the original POSSUM system was more accurate[3].

In the original POSSUM paper the methodology used to analyse results was not given and it was, therefore, not open to critical review. In a recent article the exponential model of analysis used for POSSUM clearly demonstrated the unwieldy nature of this analysis[2]. POSSUM was used to predict the probability of death for a patient group but could not be applied to individual patients.

P-POSSUM uses a well validated statistical method, which is similar to the linear model described by Wijesinghe *et al.*[2], but easier to apply. A distinct advantage of P-POSSUM compared with POSSUM is the use of discriminant analysis that can be used to ascribe risks to individual patients as opposed to groups of patients. This may make the P-POSSUM analysis more useful in every day surgical practice.

Both systems appear to be equally effective in predicting operative mortality provided the correct methodology is used. The most recent NCEPOD (National Confidential Enquiry into Perioperative Deaths) report[4] suggests the use of POSSUM to highlight 'poor risk cases' in oesophageal surgery, but investigators should be aware of the limitations associated with the exponential analysis.

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1 Whiteley MS, Prytherch DR, Higgins B, Weaver PC, Prout WG. An evaluation of the POSSUM surgical scoring system. *Br J Surg* 1996; **83**: 812–15.
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Author's reply

Sir

We thank Mr Tekkis and colleagues for their interest. The statement that the original POSSUM is more accurate when the exponential analysis is used is making a comparison using the exponential analysis to predict outcomes based on the P-POSSUM-derived risks. It is not making any comment on the accuracy of the two methods overall. We would not differ with the conclusion of Wijesinghe *et al.*[1] that 'both POSSUM and P-POSSUM are good predictors ... if the correct analysis is used for each system'.

We are somewhat concerned by the suggestion that P-POSSUM be used in day-to-day surgical practice for predicting an individual's risk. The POSSUM system has been designed as an audit tool. Neither it, nor P-POSSUM, is sufficiently accurate or specific to predict the risk of an individual and to be safely used as the basis for clinical decision making. It may give an indication that a patient is 'high-risk' after operation (the risk cannot be calculated before operation) and guide appropriate placement of the patient, for example in a high-dependency unit. We feel it would be unwise to allow these predicted risks to outweigh clinical judgement in determining any individual patient's treatment.

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1 Wijesinghe LD, Mahmood T, Scott DJA, Berridge DC, Kent PJ, Kester RC Comparison of POSSUM and the Portsmouth predictor equation for predicting death following vascular surgery. *Br J Surg* 1998; 85· 209–12.

Intraoperative lymphatic mapping and the sentinel node concept in colorectal carcinoma

Sir

We read with interest the recent article on lymphatic mapping and sentinel node biopsy in colorectal carcinoma by Joosten *et al.* (*Br J Surg* 1999; **86**: 482–6). Although we share the view that a cautious approach is required in extrapolating the technique to colorectal carcinoma, we must disagree with the comment that the concept is only applicable in a limited subset of skin derived cancers as this is not supported by presently available evidence. The sentinel node is defined as the node(s) receiving direct lymphatic drainage from a primary tumour. Joosten *et al.* have retrieved all nodes (up to 16) that took up blue dye and called them sentinel nodes, which is contrary to the concept. It is well recognized that the blue dye moves progressively from one node to the other resulting in staining of most nodes in the lymphatic basin.

We, with others[1,2], have reported that the false-negative rate of sentinel node histology increases in the presence of gross involvement of lymph nodes in the lymphatic basin; due to the diversion of lymphatic flow as a result of replacement of the sentinel node with metastatic carcinoma. Therefore, seven of 12 patients who had a false-negative sentinel node biopsy were not suitable for this technique.

The authors describe two patients with micrometastasis which we believe is significant. Liefers *et al.*[3] showed that molecular detection of micrometastasis is a prognostic tool in stage II colorectal cancer.

This field is evolving and further studies are required to confirm these data before the concept of sentinel node biopsy in colorectal carcinoma is completely disregarded.

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1 Keshtgar MRS, Waddington WA, Lakhani S, Ell PJ. *The Sentinel Node in Surgical Oncology*. Springer· Heidelberg, 1999: 164–7.
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Author's reply

Sir

We thank Messrs Keshtgar, Amin and Taylor for their reaction. We would like to see the sentinel node concept apply in tumours other than melanoma, breast, penis or vulva, but no proof for this has been published. We agree with the definition of the sentinel node, were fully aware of it at the time of writing the article and never called the blue nodes sentinel nodes, as the attentive reader will have noted.

Being aware of the problems when there is massive lymph node involvement (as pointed out in the discussion), we decided to include the patients with enlarged nodes as this was one of the first published studies to explore this concept in colonic cancer.

The relevance of micrometastatic disease is still a matter for debate, but we too considered it important enough to search for micrometastases.

Undeniably, only the first word has been said on the sentinel node concept in visceral tumours. We look forward to other studies.

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Randomized clinical trial of laparoscopic *versus* open inguinal hernia repair

Letter 1

Sir

I read with interest the paper by Juul and Christensen (*Br J Surg* 1999; **86**: 316–19) reporting a randomized trial comparing transabdominal preperitoneal (TAPP) with open inguinal hernia repair.

In the discussion the authors point out that 'in a previously published multicentric trial the laparoscopic procedure was compared with a suboptimal open surgery group'. Notwithstanding, in 23 patients belonging to the open group in the present authors' series simply a 'sutured closure of the internal ring' was performed. As these patients were adults, can this be regarded an adequate repair? One wonders how many of the three early recurrences seen in the open surgery group belonged to this subgroup. A previous prospective randomized study has demonstrated the long-term recurrence rate after high ligation of sac combined with closure of the internal ring to be as high as 34 per cent[1].

Furthermore, the authors have chosen to use polydioxanone for the Shouldice repair in preference to a non-absorbable suture. Again, in a prospective randomized study this practice has been shown to be associated with a higher recurrence rate when compared with the use of non-absorbable suture material[2].

Comparing a group of patients having open hernia dealt with by less than optimal methods with a group having laparoscopic preperitoneal mesh repair amounts to comparing apples and oranges. The technical considerations may not matter when comparing early outcome measures such as postoperative pain and length of recovery, but may influence the comparison of long-term recurrence rates between the groups.

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1 Beets GL, Oosterhuis KJ, Go PM, Baeten CG, Kootstra G. Long term follow-up (12–15 years) of a randomized controlled trial comparing Bassini–Stetten, Shouldice, and high ligation with narrowing of the internal ring for primary inguinal hernia repair *J Am Coll Surg* 1997; **185**: 352–7.

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Letter 2

Sir

The trial by Juul and Christensen compares laparoscopic repair with a muscle-stitching operation ('modified Shouldice') in healthy adults. There is, however, abundant evidence that tension-free repairs using mesh reinforcement of the posterior wall provide results in many respects superior to the Shouldice repair[1]. A more meaningful trial would be a comparison of laparoscopic and open mesh repairs. Moreover, the series is selective: patients over 75 years and those with serious cardiopulmonary or neurological illness are not included (10 and 7 per cent respectively in our series), groups in whom local anaesthesia is specifically indicated.

The reported advantages of laparoscopic repair in this study were reduction of immediate postoperative pain and shorter time (13 days) before return to normal activities. The former is widely reported[2], the latter is no better than our experience of office and manual workers having open mesh repair who returned to work in 7 and 13 days respectively[3].

Thus, the advantage of laparoscopic repair is marginal, less pain in 25 per cent of patients in the first 2–3 days. We question the justification for undertaking an expensive and invasive operation taking significantly longer to complete, using general anaesthesia and with well documented risks of serious visceral or vascular injury, when the overall results of open mesh repair under local anaesthesia are significantly better.

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Author's reply

Sir

Dr Bhandarkar questions the use of a 'sutured closure of the internal ring' as an adequate repair in adults. As stated in the paper, it was used in 23 patients who each had a small indirect hernia and an intact inguinal floor. None of these patients developed a recurrence. Dr Bhandarkar also comments on the use of an absorbable suture, but we doubt that a recurrence rate of 2 per cent after 1 year of observation could be improved by using non-absorbable suture materials.

Mr Kark and colleagues find it more meaningful to compare laparoscopic with an open mesh repair. The first patient in our trial was included in 1994 and then the Shouldice repair was regarded as the gold standard. We, therefore, compared the new procedure with the best proven conventional method. Other prospective studies have compared laparoscopic with open mesh repair and found that the time for return to normal activity and work are shorter in patients receiving laparoscopic repair[1,2].

We do not agree that there is substantial evidence to justify the statement from Kark *et al.* that open mesh repair is a significantly better operation than the Shouldice and laparoscopic repairs. These methods need evaluation in clinical trials to find the optimal treatment for each hernia in different patients. We have to master more than one technique.

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Highlights from International Workshops on Therapeutic Endoscopy (CD-ROM)

J. Y. W. Lau, J. J. Y. Sung and S. C. S. Chung (eds)

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Neoplasms of the Digestive Tract. Imaging, Staging and Management

M. A. Meyers (ed.)

285 × 220 mm Pp. 587 Illustrated 1998 Philadelphia, Pennsylvania. Lippincott-Raven US$185

Over the past few decades, new developments in both imaging procedures and treatment modalities for neoplasms of the digestive tract have led to earlier recognition and better outcome of these diseases. This book comprises all aspects of the complex variety of diseases. That it is a comprehensive work becomes obvious from its structure. The chapters are organized according to the anatomical regions (oesophagus, stomach, small bowel, colon, liver, pancreas and biliary tract) of the digestive tract. Each chapter begins with an overview of anatomy, imaging, staging and treatment. The section that follows delineates established diagnostic tools. Finally, treatment options are discussed with respect to surgery, radiation and chemotherapy, with emphasis on a multidisciplinary approach. The book finishes with an overview on upcoming diagnostic tools such as nuclear medicine and various biopsy techniques. It is a hybrid medical textbook written by experts from different fields, such as radiology, oncology and surgery, and so it contributes a great deal to a better interdisciplinary understanding. Its focus is on imaging and diagnosis. The illustrations are well chosen and detailed enough to give a clear understanding about routine findings, but there are also pitfalls. The volume is an ideal source for all clinicians working in the holistic field of (surgical) oncology and is a must for every physician with a main interest in oncology.

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Current Review of Minimally Invasive Surgery

D. C. Brooks (ed.)

284 × 220 mm. Pp. 234 Illustrated 1998 New York Springer £120

Considering the currently available books on the subject, this one really exhibits a *current* review of laparoscopic surgery. Going through the contents, an impressive number of chapters seems to cover not only a variety of traditional laparoscopic procedures, but also subjects such as anaesthetic considerations, application of the laparoscope in parathyroid and thyroid surgery, paediatric surgery and urology, gasless laparoscopy, virtual reality and medicolegal perspectives of laparoscopic surgery. The chapter 'Minimally Invasive Vascular Surgery' even deals with endovascular techniques to repair aneurysms. In general, the author's personal experiences with laparoscopic procedures are described and complemented with data from the literature. Considerable overlap exists in some of the chapters, which contrasts with other chapters that are rather short and superficial (for example, laparoscopic colon and bowel surgery). Of particular interest are the chapters on anaesthetic considerations relating to minimally invasive surgery and medicolegal perspectives on laparoscopic surgery. In conclusion, this book is excellent for the surgical trainee who wishes to be brought up to date with what is going on in laparoscopic surgery. However, the more experienced laparoscopist will only occasionally find the detailed technical information for which he or she seeks.

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Minimally Invasive Surgery. Principles and Outcomes

C. A. Andrus, J. M. Cosgrove and W. E. Longo (eds)

285 × 220 mm. Pp 400 Illustrated 1998. Amsterdam. Harwood Academic £83

One of the objectives of this all-American multiauthor book was to concentrate on outcomes from various minimally invasive procedures. In this respect the authors have been somewhat successful, although unfortunately there are no references beyond 1996 which means the work is already dated. This is rather typical of many books dealing with this rapidly advancing field. Of the 36 chapters, none deals with basic techniques, instrumentation or safety. The reader will not be able to carry out the procedure dealt with in many chapters and will need to obtain further knowledge. For example, adrenal surgery is dealt with in only one paragraph and the chapter on laparoscopic exploration of the common bile duct is quite out of date. Furthermore, many of the subspecialty areas are described very briefly. In the reviewer's opinion it is time that authors of minimally invasive surgery textbooks concentrated on site-specific areas rather than trying to write comprehensive books that inevitably are superficial in many fields. Nevertheless, there are some good chapters here, especially those dealing with fundoplication, transanal endoscopic microsurgery and discectomy. This book will probably be of value only as a reference text.

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Surgical Ethics

L. B. McCullough, J. W. Jones and B. A. Brody (eds)

240 × 160 mm. Pp. 396 Not illustrated 1998. New York Oxford University Press £35.

This is a multiauthor publication from the USA. The topics covered are similar to those in *The Surgeons Duty of Care (The Senate of Surgery of Great Britain and Ireland, 1997)*, but with a depth of philosophical background and extension into clinical examples. There are inevitable differences but generally these are instructive. Rather than the expected reliance on defensive medicine, a policy of 'preventive ethics' is advocated, based on establishing a good, honest surgeon–patient relationship. Consent to treatment is taken seriously, indicating the change that is coming in the UK. There is a superb, compassionate chapter on care of the dying. Unsurprisingly, resource issues are dominated by systems of reimbursement rather than waiting lists, with the exception of transplantation. However, the discussion is thought-provoking in the context of NHS trusts, primary care groups and potential conflicts of interest. This book is more than a statement of ethics as applied to surgery, it is also a discussion of many current issues in the resourcing, delivery and limitations of surgical care. I know of no equivalent and recommend it strongly.

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Emergency Abdominal Surgery. 3rd ed.

P. F. Jones, Z. H. Krukowski and G. G. Youngson (eds)

243 × 171 mm. Pp 556. Illustrated. 1998. London Chapman and Hall. £45

The third edition of this book has recently appeared in print. Sixteen of the 20 authors come from Aberdeen, with two from South Africa and two from the USA. Nevertheless, the book gives a concise picture of what may be regarded as international practice in the management of the acute abdomen. One can still, however, occasionally come across statements such as 'it is now universal practice to obtain a normal T-tube cholangiogram before withdrawing the tube on the 12th postoperative day' after biliary tract surgery. In most parts of Europe the postoperative cholangiogram is done much earlier, at most 5 days after operation. The authors cover the topic of abdominal emergencies from a general point of view and so include urological and gynaecological emergencies, as well as the acute abdomen in pregnancy and the puerperium. A special section is directed to emergency abdominal surgery in infancy and childhood. It would also have been advisable to include a section on the specific clinical problems related to the acute abdomen in the geriatric population It is obvious that the authors overall are experienced clinicians; their advice and statements are authoritative The references are appropriate and up to date, with many published during the 1990s The illustrations are generally informative while retaining simplicity. Surgical trainees will benefit from reading this worthwhile book. However, it is preferable that they do this before the patient comes to the hospital, rather than use the volume as an emergency-room manual.

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Scientific Surgery

Kopelmann D, Klemm O, Bahous H, Klein R, Krausz M, Hashmonai M. Postoperative suction drainage of the axilla: for how long? Prospective randomised trial. *Eur J Surg* 1999; **165:** 117–20.

Ninety women were studied after axillary dissection for breast cancer. Removal of drains after 3 days resulted in a higher seroma rate (nine of 42) than leaving them until drainage ceased (two of 48, $P < 0{\cdot}02$). No seroma resulted in the first group if there was less than 250 ml drainage during the first 3 days.

Bozorgzadeh A, Pizzi WF, Barie PS, Khaneja SC, LaMaute HR, Mandava N *et al.* The duration of antibiotic administration in penetrating abdominal trauma. *Am J Surg* 1999; **177**; 125–31.

Some 314 consecutive patients were randomized to 24 h or 5 days of intravenous cefoxitin The duration of administration had no effect on the rate of infection

Allo MD, Bennion RS, Kathir K, Thompson JE Jr, Lentz M, Meute M *et al.* Ticarcillin/clavulanate *versus* imipenem/cilistatin for the treatment of infections associated with gangrenous and perforated appendicitis. *Am Surg* 1999; **65:** 99–104.

Some 137 patients randomized to 3–5 days treatment with one of these regimens. Infection rates and outcomes were similar.

Urbach DR, Kennedy ED, Cohen MM. Colon and rectal anastomoses do not require routine drainage: a systematic review and meta-analysis. *Ann Surg* 1999; **229:** 174–80.

Four randomized trials including 414 operations were evaluated. The trials were generally limited quality but there appeared no advantage for routine drainage

Kissmeyer-Nielsen P, Jensen MB, Laurberg S. Perioperative growth hormone treatment and functional outcome after major abdominal surgery: a randomised, double-blind, controlled study. *Ann Surg* 1999; **229:** 298–302.

Twenty-four patients having ileorectal pouch surgery were studied Growth hormone significantly increased muscle strength at 10, 30 and 90 days after operation

Benoist S, Panis Y, Denet C, Mauvais F, Mariani P, Valleur P. Optimal duration of urinary drainage after rectal resection – a randomised controlled trial. *Surgery* 1999; **125:** 135–41.

In a study of 126 patients randomized to 1 or 5 days catheterization the rates of subsequent retention (25 *versus* 10 per cent respectively) and urinary infection (20 *versus* 42 per cent) were significantly different. Removal of the catheter after 1 day was recommended for all except those having surgery for low rectal cancer

Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. *Arch Surg* 1999; **134:** 170–6.

In critically ill patients, selective decontamination significantly reduced mortality more effectively in surgical (odds ratio 0·7, 95 per cent confidence intervals 0·52–0·93) than in medical patients (0·91, 0·71–1·18).

Colucci G, Maiello E, Gebbia V, Giuliani F, Serravezza G, Lelli G *et al.* 5-fluorouracil and levofolinic acid with or without recombinant interferon-2b in patients with advanced colorectal carcinoma: a randomised multicenter study with stratification for tumor burden and liver involvement by the Southern Italy Oncology Group. *Cancer* 1999; **85:** 535–45.

The addition of interferon failed to improve survival (median 11 months *versus* 12 months with interferon) but significantly worsened toxicity in the 204 patients studied

Badwe RA, Sharma V, Bhansali MS, Dinshaw KA, Patil PK, Dalvi N *et al.* The quality of swallowing for patients with operable esophageal cancer: a randomized trial comparing surgery with radiotherapy. *Cancer* 1999; **85:** 763–8.

Some 99 patients with a squamous carcinoma were included. Surgery resulted in significantly improved swallowing after 6 months ($P = 0{\cdot}03$) and better survival (odds ratio 2·74, 95 per cent confidence interval 1·51–4·98) than radiotherapy

Hooker GD, Plewes EA, Rajgopal C, Taylor BM. Local injection of bupivacaine after rubber band ligation of hemorrhoids: prospective randomised study. *Dis Colon Rectum* 1999; **42:** 174–9.

Some 115 patients were randomized to bupivacaine, saline or no injection After 6,12 and 48, no advantage was seen. After 30 min bupivacaine caused a significant reduction in reported pain, nausea and shaking.

Chiu J-H, Chen W-S, Chen C-H, Jiang J-K, Tang G-J, Lui W-Y *et al.* Effect of transcutaneous electrical nerve stimulation for pain relief on patients undergoing hemorrhoidectomy: prospective, randomised, controlled trial. *Dis Colon Rectum* 1999; **42:** 180–5.

Perioperative use of TENS significantly improved pain scores up to 24 h and reduced morphine use in the 60 patients studied.

Ho Y-H, Seow-Choen F, Leong A, Eu K-W, Nyam D, Teoh M-K. Randomised controlled trial of low molecular weight heparin *versus* no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. *Dis Colon Rectum* 1999; **42:** 196–202.

In the 320 patients included, LMWH significantly reduced the rate of postoperative DVT (3 per cent *versus* none), and there was no corresponding major increase in bleeding complications (1·8 *versus* 6·7 per cent respectively).

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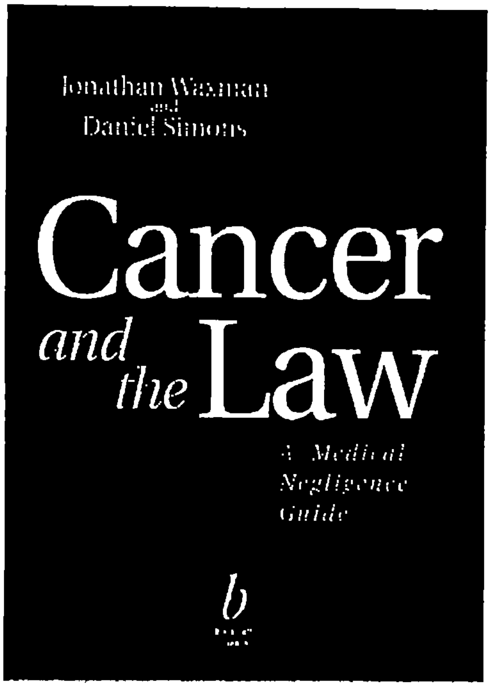

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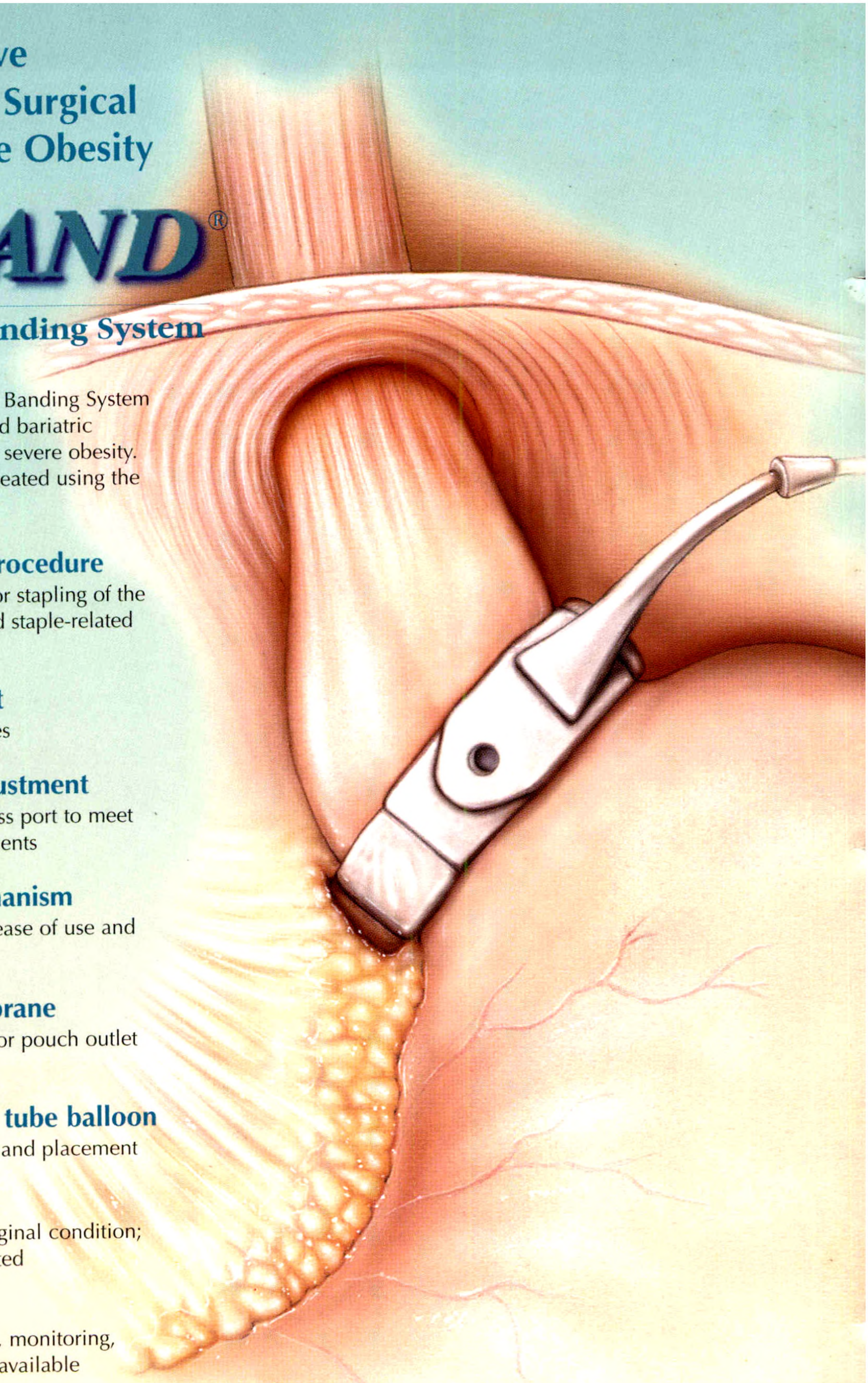

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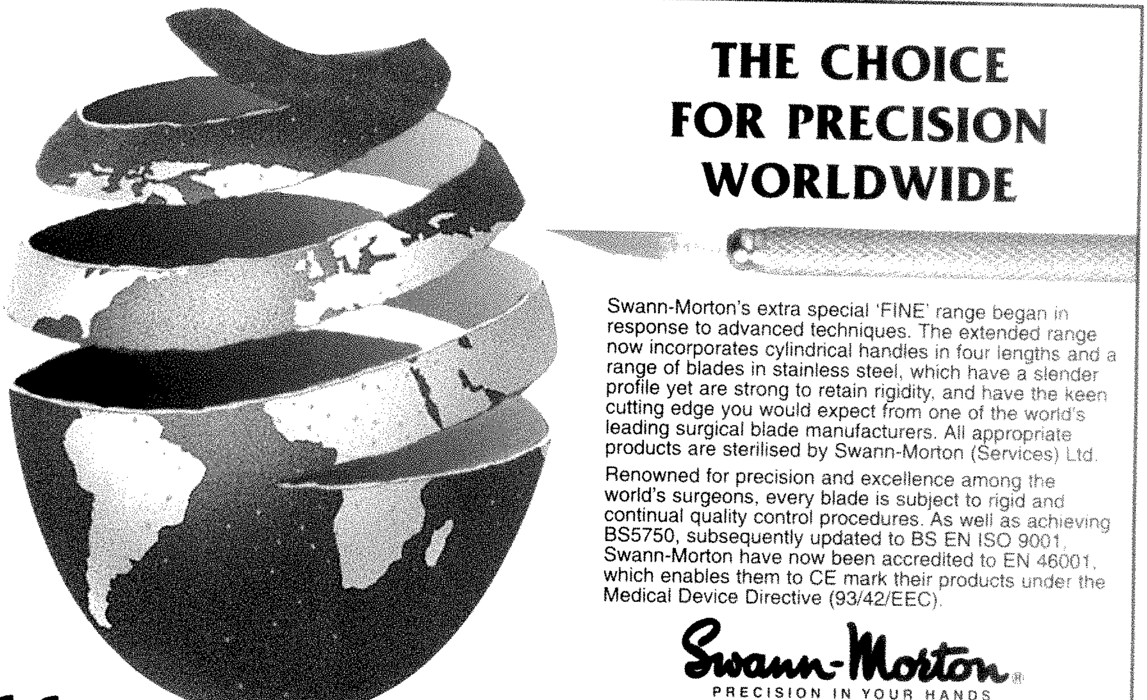

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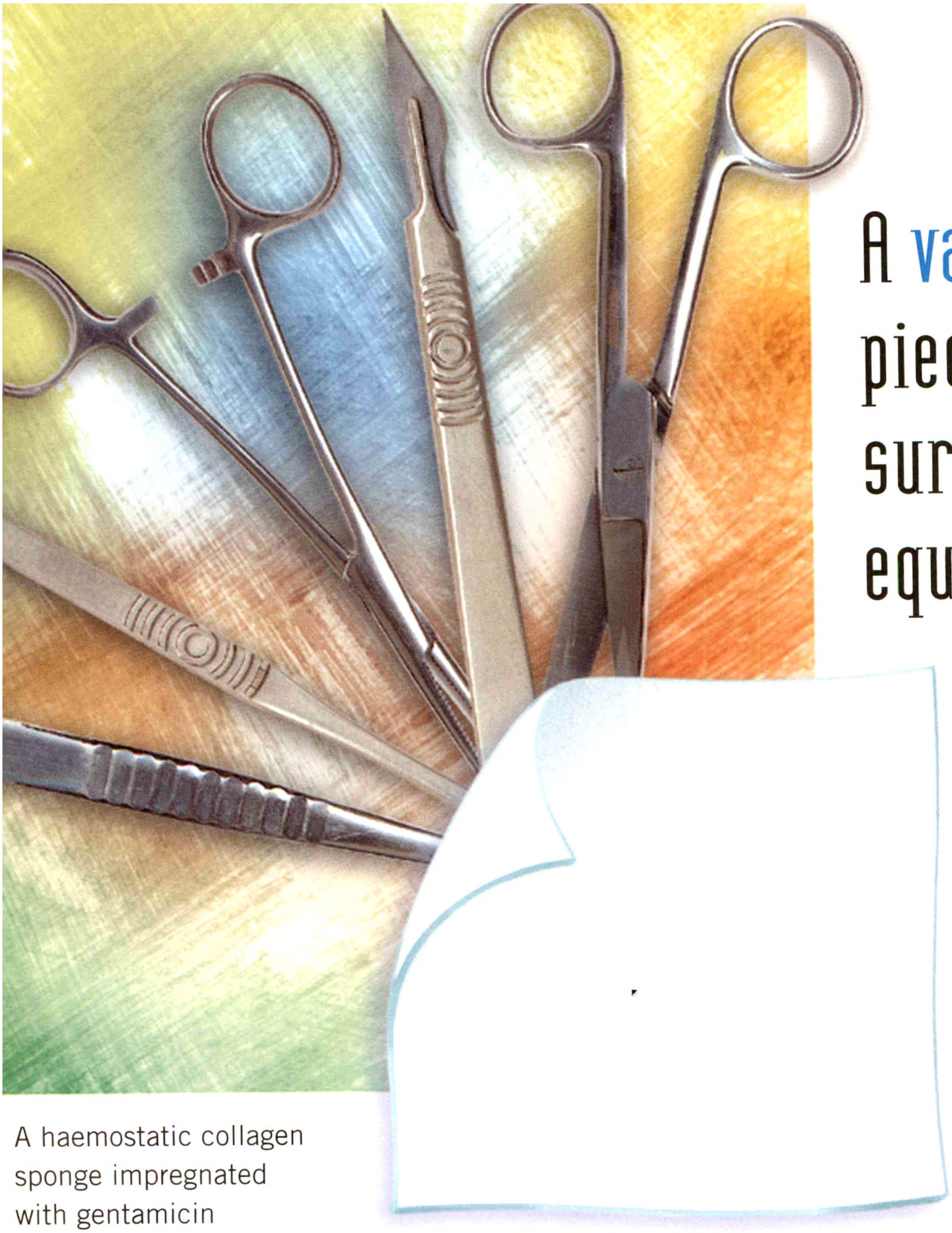

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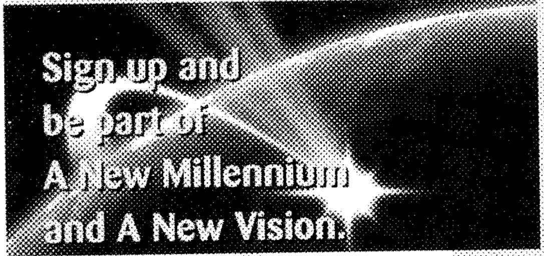

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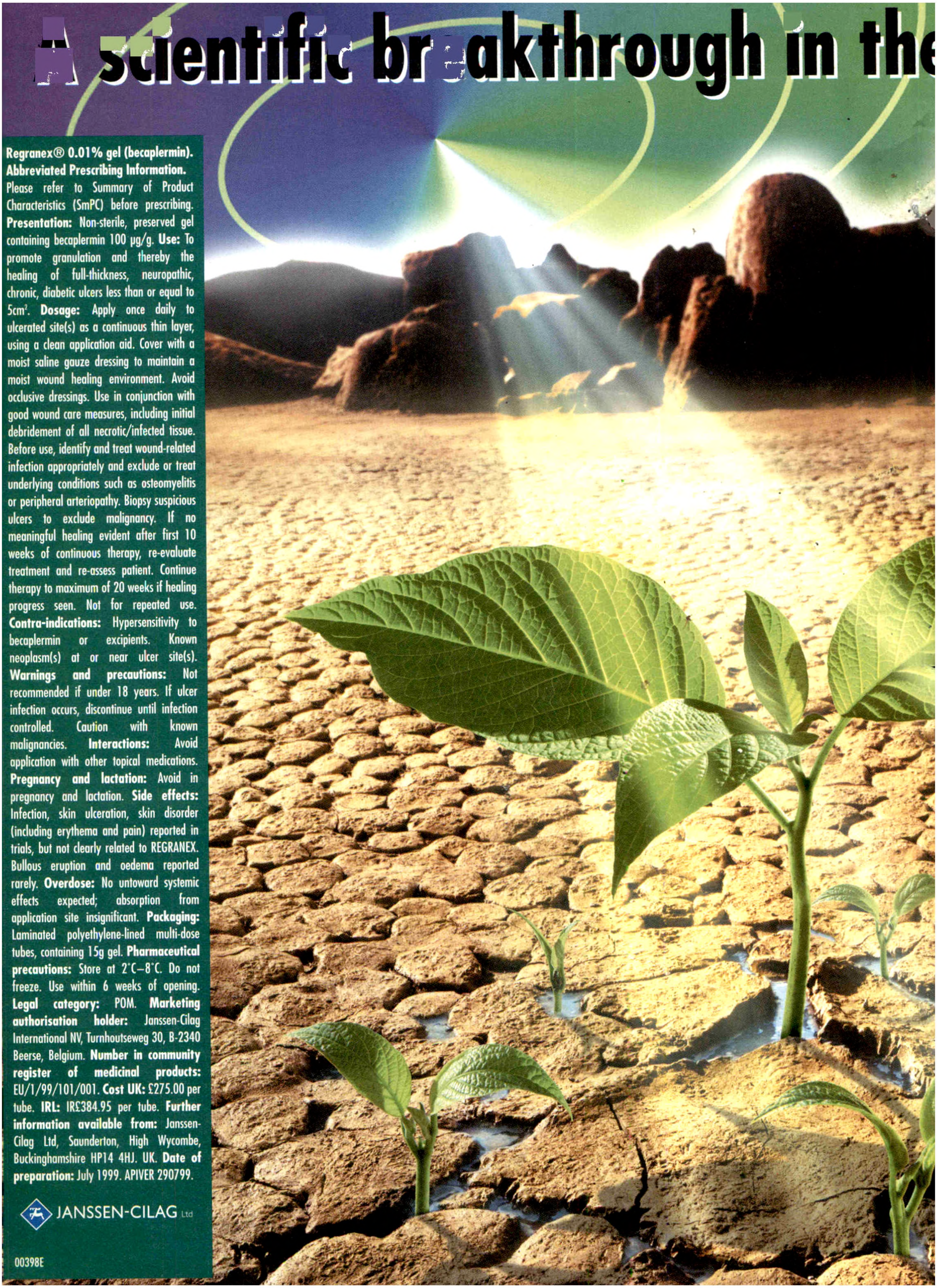
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Adjuvant radiotherapy for rectal cancer

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Colorectal cancer is the second commonest cause of death from malignancy in the Western world. In the UK each year there are approximately 28 000 cases, and 19 000 deaths are attributable to the disease[1]. Rectal cancer represents a specific problem: in population-based studies a significant proportion of patients is noted to develop local recurrence despite an apparently curative resection. These recurrences are usually associated with severe local symptoms, are difficult to palliate adequately and lead to a miserable death.

There is now strong evidence from randomized controlled trials that both postoperative and preoperative radiotherapy reduce local recurrence and may also reduce the number of cancer-related deaths. In the Medical Research Council's MRC CR03 trial, patients with mobile rectal cancers were randomized to surgery alone or surgery plus postoperative radiotherapy (40 Gy over 4 weeks). There was a statistically significant reduction in local recurrence in the latter group[2]. There is also some evidence to suggest that combined radiation and chemotherapy may be superior to radiotherapy alone. In the United States a small but highly influential trial, in which patients were randomized to postoperative radiotherapy alone or radiotherapy with sequential and concurrent chemotherapy, demonstrated a statistically significant reduction in local recurrence associated with combined therapy[3]. In a subsequent larger trial patients were randomized between two different chemotherapy regimens during radiotherapy.

Both the MRC CR03 and the American trials demonstrated a statistically significant improvement in disease-free survival rate[3,4]. However, there are a number of disadvantages to the use of postoperative radiotherapy. Surgical complications may delay or even prevent the start of radiotherapy, and there is a risk of radiation-induced complications including small bowel stricture. There may also be increased acute toxicity when chemotherapy is combined with radiotherapy. As an alternative strategy, a short course of preoperative radiotherapy has been tested extensively in Scandinavia. In the Swedish Rectal Cancer Trial 1168 patients were randomized to receive preoperative radiotherapy (25 Gy over 1 week) followed by surgery or to have surgery alone. This trial demonstrated a highly statistically significant reduction in local recurrence and a 10 per cent absolute improvement in overall survival for patients who received preoperative radiotherapy (none of whom received adjuvant chemotherapy)[5]. Although these are clearly impressive results, the disadvantage of this approach is that the lack of patient selection results in many patients receiving adjuvant radiotherapy unnecessarily.

Since the completion of these studies there have been a number of observations that might influence interpretation of the results. First, improvements in surgical technique, in particular the adoption of total mesorectal excision (TME), have already led to single-surgeon reports of local recurrence rates following resection that are considerably lower than any of the recurrence rates reported in the surgery-alone arms of previous randomized trials evaluating adjuvant radiotherapy[6,7]. Second, there is an increasing awareness of the mechanism involved in the development of local recurrence. The demonstration that microscopic involvement of the circumferential resection margin predicts a high risk of local recurrence provides a new, refined method of selecting patients who require postoperative radiotherapy[8]. It is recognized that adjuvant radiotherapy impairs functional outcome. A small retrospective study has highlighted adverse function after postoperative chemoradiotherapy[9]. Furthermore, the recent publication describing a small subgroup of patients from the Swedish Rectal Cancer Trial demonstrates that a short course of preoperative radiotherapy produces similar functional impairment[10].

The Dutch Colorectal Group is currently conducting a trial in which patients undergo TME with either routine preoperative short-course radiotherapy or initial surgery and postoperative radiotherapy given only to patients with involvement of the circumferential resection margin. The MRC CR07 trial has a similar design but is more pragmatic. It does not insist on TME; it incorporates the use of concurrent chemoradiotherapy after operation (with some modifications to reduce acute toxicity), and it allows systemic chemotherapy to be given according to local practice. As well as addressing the important endpoints of local recurrence and survival, the use of validated quality-of-life questionnaires administered to all patients should provide essential prospectively collected information on outcome which hitherto has been lacking in trials of adjuvant radiotherapy. The CR07 trial thus offers an important opportunity to define the most appropriate adjuvant radiotherapy policy for patients in the UK with operable rectal cancer.

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Retrosternal goitre

Problematic situations are discussed in the 'Clinical dilemma' section. The Editors wish to encourage the BJS readership to play a part here. If you have a 'dilemma' that can be expressed as a question (not more than 40 words), let us know by contacting the BJS office. You may even have thoughts on a suitable expert to voice an opinion. The most interesting problems will be followed up in this section of the Journal in the coming months.

In this issue of BJS a dilemma related to thyroid surgery is highlighted. What does one do if difficulty is encountered delivering a retrosternal goitre? How should this situation be handled? Professor Malcolm Wheeler of Cardiff replies.

Most retrosternal goitres can be delivered and safely resected through a standard cervical approach. Many of the principles originally defined by Kocher[1] for managing retrosternal goitres are still relevant and, provided careful attention is paid to fundamental points of technique, the operation is usually straightforward and accomplished without difficulty.

Goitres extending into the thorax frequently compress veins, causing venous engorgement and even frank superior vena cava obstruction. These effects clearly increase the difficulties and hazards of surgery. Venous pressure may be reduced and blood loss minimized if the patient is placed in a head-up position on the operating table, with the neck well extended. It is a paradox that, to gain good access to a gland extending far inferiorly, the collar incision should be placed at a level 1–2 cm higher than usual: the lower the goitre, the higher the incision. A significant retrosternal or intrathoracic gland extension requires division of the strap muscles on one or both sides in most cases. This simple measure often results in a marked improvement in surgical access. No attempt should be made to deliver the retrosternal component until the superior thyroid vessels have been carefully ligated and divided, taking the usual precautions to identify and preserve the external branch of the superior laryngeal nerve. This essential step imparts a mobility to the upper pole of the thyroid gland which will play a major role in the subsequent upward movement and delivery of the retrosternal portion into a cervical position. Any middle thyroid veins identified at this stage should be ligated and divided before attempt is made to mobilize the thoracic extension. All lateral attachments to the cervical gland are dissected free; it is then usually possible to identify the superior parathyroid gland and recurrent laryngeal nerve, the latter close to its point of entry into the larynx. The fascial attachments and adhesions to the thyroid are freed with the finger inferiorly, especially between the gland and the posterior aspect of the manubrium, while applying gentle upward traction to the thyroid with the other hand. Some sharp dissection with scissors under direct vision will usually also be required. Successful delivery of the thyroid is almost invariably achieved at this stage.

If difficulty is still encountered despite careful performance of the above steps, additional manoeuvres are necessary. The surgeon's finger should be used to sweep around the intrathoracic gland again, to confirm that all palpable adhesions have been divided. A gland extending well down to the level of the aortic arch (or even further) may not be fully reached by the tip of the finger. A sterile soup spoon can often be used to advantage; it may be slipped down alongside the anterolateral aspect of the thyroid, breaking negative intrathoracic pressure, reaching further than the finger, occupying less space and, in most instances, leading to an immediate and satisfying delivery of the gland[2].

Special care should be taken in the enthusiasm of the moment to avoid undue traction on the recurrent laryngeal nerve, which can easily be damaged at this stage in spite of prior careful identification at a higher level in the neck. Early identification of this nerve before dissection and mobilization of the retrosternal gland extension was stressed by Proye[3] in his description of the 'toboggan' technique. An alternative technique for delivering the thyroid gland is the placement of heavy silk sutures into the cervical component, applying upward traction and placing more sutures in series as the retrosternal extension gradually comes into view. Obviously this technique has limited application when there is a soft friable colloid goitre. Care should always be taken to avoid breaching the capsule of the gland in case there is unsuspected malignancy, and so the older technique of intracapsular fragmentation (morcellation) is to be condemned. Tumour spillage and major bleeding may well be undesired side-effects. The surgeon should be aware of the fact that the incidence of tumour in an impalpable retrosternal goitre may be in excess of 10 per cent[4].

Sometimes, in spite of performing all of these procedures and imparting reasonable mobility to the thyroid, the offending lobe still cannot be brought into the neck as there appears to be too little room to manoeuvre. In these circumstances the opposite thyroid lobe, which may well be normal in size and in a cervical position, should be excised to provide more room in the neck. This generally facilitates the successful completion of surgery.

If no progress is made even after carrying out all of the above, a complete sternotomy and mediastinal approach is required. This technique, popularized originally by Dunhill[5] and later by Taylor[6], is rarely necessary, but it is needed for extraordinarily large intrathoracic goitres where the thoracic inlet may be too small for delivery, for tumours with significant invasion and when excessive uncontrollable bleeding is encountered[7]. The rare truly ectopic intrathoracic gland, with its major blood supply derived from intrathoracic vessels, also dictates this approach.

The so-called crossed substernal goitre is a very rare variety of retrosternal gland in which there is extension from a left-sided gland to the right mediastinum. Such glands, although usually retrievable through the neck, occasionally require a right anterolateral thoracotomy through the fourth interspace to allow adequate exposure and dissection.

In summary, therefore, most retrosternal goitres can be resected through an entirely cervical approach with a low complication rate. On rare occasions a median sternotomy will be required to permit a safe and complete thyroidectomy.

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Evidence that metastasis is less common in cirrhotic than normal liver: a systematic review of post-mortem case–control studies

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Background: It has been hypothesized that the cirrhotic liver is afforded protection against metastasis. The evidence has been examined and the plausibility of such a phenomenon is reviewed.
Methods: A systematic literature review was conducted with analysis of combined data from post-mortem case–control studies.
Results: Overall, the crude rate of metastasis to normal liver was 37·3 per cent, while the rate to cirrhotic liver was 23·7 per cent. The Mantel–Haenszel (MH) fixed-effects estimate of the odds ratio was 0·47 (95 per cent confidence interval (c.i.) 0·41–0·53; $\chi^2 = 136$, 11 d.f., $P < 0{\cdot}001$). The DerSimonian–Laird (DL) random-effects estimation of the odds ratio was 0·42 (95 per cent c.i. 0·31–0·58; $\chi^2 = 28$, 1 d.f., $P < 0{\cdot}001$). For tumours arising within the distribution of the portal vein, the crude rate of metastasis to normal liver was 47·6 per cent, whereas the rate to cirrhotic liver was 29·8 per cent. The MH estimate of the odds ratio was 0·45 (95 per cent c.i. 0·37–0·54; $\chi^2 = 68{\cdot}2$, 5 d.f., $P < 0{\cdot}001$). The DL pooled odds ratio was 0·44 (95 per cent c.i. 0·28–0·70; $\chi^2 = 12{\cdot}3$, 1 d.f., $P < 0{\cdot}001$). The MH and DL pooled estimates of the odds ratio were similar for groups of patients from the East (Japan) and the West (Europe and the USA).
Conclusion: The post-mortem evidence reviewed suggests that the likelihood of metastasis to the cirrhotic liver is lower than that to normal liver. The degree of protection for tumours arising from within the distribution of the portal vein is neither greater nor less than it is overall. Eastern and Western populations appear to have a similar degree of risk reduction. The differences noted were significant on testing in the meta-analysis, but confounding bias accounting for these differences has not been excluded.

Paper accepted 28 May 1999

British Journal of Surgery 1999, **86**, 1237–1242

Introduction

It is over 100 years since it was suggested that the cirrhotic liver is protected from the development of metastasis from tumours outside the liver[1], but the phenomenon has received little attention. The protective effect of cirrhosis was generally accepted, as reflected by the occasional case report of metastasis in the cirrhotic liver, emphasizing its rarity. The aetiology of cirrhosis differs in Eastern and Western hemispheres, due mainly to a 10–20-fold difference in the prevalence of hepatitis B carriage[2–4]; cirrhosis from this cause is more common in the Eastern hemisphere. The mortality rate from colorectal cancer in the UK population is 2·3–3·1 times that in the Japanese[5]. A recent study of 250 Japanese patients with colorectal cancer found that none of 46 patients with cirrhosis had metastasis at presentation while 20 per cent of the non-cirrhotic group had metastasis[5]. The published results of individual post-mortem studies on the phenomenon provide supporting evidence, but most contain too few patients with the combination of cirrhosis and malignancy for conclusive statistical analysis.

Materials and methods

Selection of papers

Post-mortem studies were sought for inclusion by search of Medline, BIDS (Bath Information and Data Services) EM Base, and BIDS Science Citation Index from 1963 to the present. The search terms used were 'liver cirrhosis', 'liver neoplasms (secondary)' and 'liver metastasis'. Sets were combined using the logic function 'and'. The references of the primary sources were examined for further citations. Inclusion criteria were post-mortem studies, which identified the rates of metastasis to the liver from extrahepatic primary tumour in cirrhotic and non-cirrhotic livers or both. Inclusion criteria for analysis were post-mortem case–control studies, which gave the rates of metastasis to normal and cirrhotic liver in the presence of malignancy with metastatic potential. There were no universal criteria for the diagnosis of cirrhosis. Cases of biliary cirrhosis due to obstruction by tumour were excluded from analysis. Cases of primary hepatic cancer were excluded, as were malignancies without metastatic potential. The papers were ascribed equal weighting for quality of method, as all were individual post-mortem series. They were reviewed individually and data extracted. Most gave sparse details of the whole population, so it was not possible to examine or test for heterogeneity on the basis of differences in population demographics or primary tumour location for all of the studies.

Statistical methods

Publication bias was tested for in a funnel plot (*Fig. 1*). To determine the size of studies, the numbers of patients with both cirrhosis and cancer of metastatic potential were used. This was because the ratio of controls to cases varied widely; inclusion of excessively large numbers of controls alone does not add much additional power to a study, despite increasing its size. The ratio varied between 1·6 : 1 and 122 : 1. For each data set (summarized in *Table 1*) a 2 × 2 contingency table was laid out. The odds ratio (OR) was calculated. The pooled OR was determined, in a fixed-effects model, using the statistical analysis method described by Mantel and Haenszel (MH)[6,7]. The DerSimonian–Laird (DL) method[8] was used as the random-effects model.

Where the papers gave details of the location of the primary tumours, this information was used to gather data on the specific effect of tumours within the portal distribution. In this analysis the oesophagus was considered to be outside the distribution of the portal vein. The data are summarized in parentheses in *Table 1*. The studies could be divided into those performed in the Western hemisphere (Europe and the USA) and those carried out in Japan. These subsets were analysed separately to explore heterogeneity due to differing aetiology of cirrhosis or population effects.

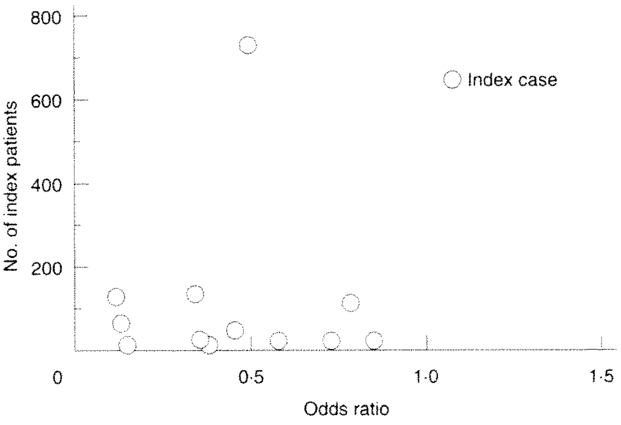

Fig. 1 Funnel plot testing publication bias. Index cases are those with cirrhosis and carcinoma

Table 1 Summary of data on cirrhosis and metastasis in patients with malignancy extracted from the papers examined

		Metastasis in cirrhosis cases		Metastasis in controls	
Reference	Location	No	Yes	No	Yes
Colwell[15]	UK	25 (4)	2 (0)	1926 (285)	608 (186)
Fisher *et al.*[16]	USA	17 (4)	11 (2)	473 (113)	417 (77)
Gall[17]	USA	62	7	117	101
Goldstein *et al.*[18]	USA	19 (5)	12 (1)	35 (3)	26 (9)
Hamaya *et al.*[19]	Japan	543 (250)	194 (114)	11 352 (4641)	8199 (4841)
Lieber[20]	USA	83 (2)	6 (1)	3636 (83)	1456 (37)
Lisa *et al.*[21]	USA	16	3	408	204
Melato *et al.*[22]	Italy	112 (38)	26 (12)	128 (62)	88 (88)
Melato *et al.*[22]	Japan	19	3	191	204
Norkin *et al.*[23]	USA	84 (39)	37 (23)	1821 (732)	985 (591)
Ruebner *et al.*[24]	USA	43	11	69	39
Vanbockrijck and Kloppel[25]	Belgium	20	10	349	302

Values in parentheses are numbers of tumours within the portal distribution

Results

Seventeen papers were identified as relevant, of which six were excluded, four papers because they presented too few data for analysis[9–12] and two because they were not relevant to the study[13,14]. Eleven papers were therefore accepted for analysis[15–25] (*Table 1*); that by Melato *et al.*[22] appears twice as the study was dual-centred and the results are presented separately. All papers describe a lower rate of metastasis to cirrhotic liver than to normal liver. The study by Hamaya *et al.*[19] is the largest and has the greatest power. The smaller studies have ORs ranged around that of the study by Hamaya and co-workers, as would be expected, suggesting that there is little heterogeneity and that combining results is valid (*Fig. 2*).

The odds of metastasis to normal and cirrhotic liver (*Fig. 2*)

Overall, in this series, the crude rate of metastasis to normal liver was 37·3 per cent, while the rate to cirrhotic liver was 23·7 per cent. The results from the combined analysis indicate that patients with both cancer and cirrhosis have a reduced risk of hepatic metastasis, compared to those with cancer and otherwise normal livers. Using the MH fixed-effects model the pooled estimate of the OR was 0·47 (95 per cent confidence interval (c.i.) 0·41–0·53; $\chi^2 = 136$, 11 d.f., $P < 0{\cdot}001$). In the random-effects model the pooled OR was 0·42 (95 per cent c.i. 0·31–0·58; $\chi^2 = 28$, 1 d.f., $P < 0{\cdot}001$). The 'combinability' for OR (Q) was 31·81, 11 d.f., $P = 0{\cdot}0008$.

Tumours within the distribution of the portal vein (*Fig. 3*)

Seven papers gave details of the site of the primary malignancy, which allowed tumours within the portal distribution to be examined separately[15,16,18–20,22,23]. In these reports, the crude rate of metastasis to normal liver was 47·6 per cent, whereas the rate to cirrhotic liver was 29·8 per cent. In the MH fixed-effects model the OR was 0·45 (95 per cent c.i. 0·37–0·54; $\chi^2 = 68{\cdot}2$, 5 d.f., $P < 0{\cdot}001$). In the DL random-effects model the OR was 0·44 (95 per cent c.i. 0·28–0·70; $\chi^2 = 12{\cdot}3$, 1 d.f., $P < 0{\cdot}001$). The degree of protection from tumour within the portal distribution was similar to that for neoplasms elsewhere.

Japan (Eastern) and the Western world (*Fig. 3*)

The risk was the same regardless of the region of origin of the study. For Eastern studies the MH OR was 0·48 (95 per cent c.i. 0·41–0·57; $\chi^2 = 78{\cdot}9$, 1 d.f., $P < 0{\cdot}001$). In the DL random-effects model it was 0·32 (95 per cent c.i. 0·1–1·0; $\chi^2 = 3{\cdot}9$, 1 d.f., $P = 0{\cdot}49$). For the Western world the MH OR was 0·44 (95 per cent c.i. 0·35–0·54; $\chi^2 = 59{\cdot}7$, 9 d.f., $P < 0{\cdot}001$). In the DL random-effects model it was 0·42 (95 per cent c.i. 0·27–0·64; $\chi^2 = 16{\cdot}4$, 1 d.f., $P < 0{\cdot}001$).

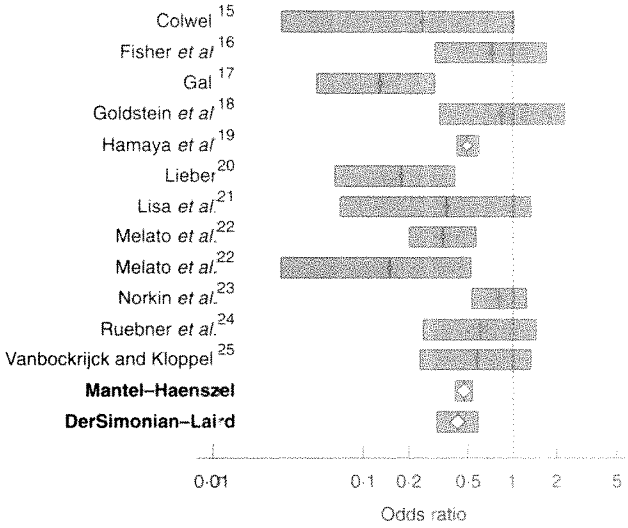

Fig. 2 Results of the individual studies and of the combined analysis (Mantel–Haenszel weighted risk). The central line for each study represents the odds ratio, the central diamond indicates the size of the study, and the box gives the 95 per cent confidence limits. Unity indicates no effect; smaller values to the left indicate a reduced incidence of metastasis, while values to the right of unity indicate increased risk

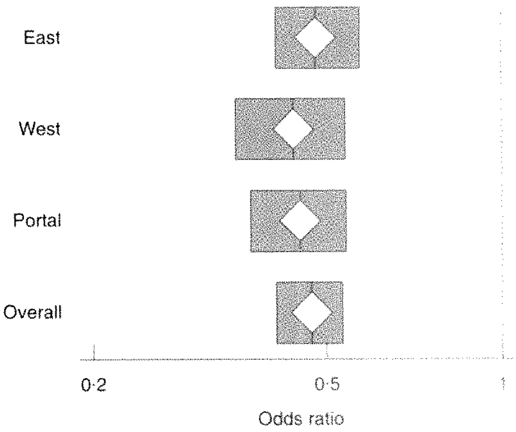

Fig. 3 Individual odds ratios for the subsets analysed. The odds ratios are the Mantel–Haenszel (fixed effects) results. The central line for each subset represents the odds ratio, the diamond size and the box give the 95 per cent confidence limits

Table 2 Numbers and rates of cirrhosis and extrahepatic carcinoma in the post-mortem series

Reference	No. of autopsies	No. with cirrhosis	No. with carcinoma
Colwell[15]	12 500	NS	3 259 (26·1)
Fisher *et al.*[16]	2 865 (men)	213 (7·4)	890 (31·1)
Gall[17]	NS	682*	218 (22·0)
Goldstein *et al.*[18]	4 166	31 (0·7)	61*
Hamaya *et al.*[19]	240 377	8 798 (3·7)	19 551 (8·1)
Lieber[20]	29 879	1 073 (3·6)	5 092 (17·0)
Lisa *et al.*[21]	6 036	NS	612 (10·1)
Melato *et al.*[22]	5 241	500 (9·5)	216*
Melato *et al.*[22]	6 511	529 (8·1)	395*
Norkin *et al.*[23]	15 713	1 268 (8·1)	2 839 (18·1)
Ruebner *et al.*[24]	23 000	399 (1·7)	399*
Vanbockrijck and Kloppel[25]	2 162	153 (7·1)	651 (30·1)

Values in parentheses are rates expressed as a percentage of the post-mortem series. *Selected cases. NS, not stated

Discussion

Exploring heterogeneity and bias

It may be noted in *Table 2* that there are differences in the apparent rates of cirrhosis and carcinoma in the individual papers. Goldstein *et al.*[18] gave a rate of cirrhosis of 0·7 per cent, whereas Melato *et al.*[22] demonstrated a rate more than tenfold greater at 9·5 per cent. The rates of carcinoma are similarly diverse, with Fisher *et al.*[16] reporting a rate of 31·1 per cent and Hamaya *et al.*[19] 8·1 per cent. This suggests a degree of heterogeneity between the papers. This review has examined post-mortem case–control studies and accepted pathologists' definitions of disease. While the pathologist's conclusion is often regarded as the 'gold standard', heterogeneity exists owing to the lack of a strict definition of cirrhosis. Other sources of heterogeneity, which cannot be excluded, relate to population demographics and the exact methods of case selection, which varied between the studies. These effects may be minimized by considering the results of the random-effects model[26].

Bias may be introduced into meta-analyses in several ways. Common to all are the problems of publication bias and location bias which, although unavoidable, must be considered by the reviewer. The present search was extended as widely as possible in electronic databases and was further extended through search of citations from all relevant documents. There were no discernible instances of repeated publication of the same data. The aim of this review was to be objective in reviewing the evidence; it was therefore decided that the papers examined would be given equal weight to avoid subjective decision-making on inclusion which would have incorporated the authors' own biases[27].

Shapiro[27] warns of the need to search for plausible sources of selection bias operating in the same direction in the studies. Ruebner *et al.*[24] give insight into a confounding bias, which may not be random and could pervade all the studies. They observed that survival in cirrhotic patients following operation for cancer was lower than that in the control group. In their series only 50 per cent of the operated cirrhotics lived more than 3 weeks after operation. Furthermore, the post-mortem population is a selection of cases and not a sample; this distinction is important because perioperative death is an indication for autopsy. The selected cirrhotic patients may not live long enough to develop metastasis with the help of surgical intervention. Thus the post-mortem series represents a selection and may not be representative of any real population. This form of selection bias cannot be excluded as a confounding influence which might explain the differences detected. Individually, each of the case–control studies is flawed by its potential biases and, if bias has the same trend in each study, it will be a feature of any meta-analysis. In the absence of other supporting evidence and a plausible explanation, the correct conclusion should disregard the statistical findings, regardless of the size of any association.

However, other sufficient supporting evidence now exists. The clinical study by Uetsuji *et al.*[5] could not have suffered from the same form of confounding bias as the other reports and adds strength to the argument for a difference related to the presence or absence of cirrhosis.

Exploring plausibility

Gall[17] determined that the aetiology of the cirrhosis was important. He noted that the cirrhosis associated with biliary obstruction due to the primary tumour was much more likely to be associated with metastasis than other forms of cirrhosis. For this reason biliary cirrhosis was excluded from the present analysis. The aetiology of cirrhosis differs between people in the Eastern and Western hemispheres; however, the present results show the ORs to be broadly similar.

The metastatic cascade provides a good framework for examining potential mechanisms of hepatic protection. The normal liver has unique structures that may favour the development of metastasis. First, the tumour cells must arrive in the liver, probably through the bloodstream, although lymphatic spread has also been postulated. The liver has a unique dual blood supply from both the hepatic artery and the portal vein. The portal blood flow ensures that the liver is the first vascular bed encountered by tumour cells spreading in the portal venous system. Sugarbaker[28] states that this ensures the liver is the favoured organ of metastasis for tumour in this distribution. Shirai *et al.*[29] have demonstrated that the location of the primary tumour affects the pattern of the lobar distribution of metastases in the liver owing to streamlined flow of blood in the portal vein. Disruption of portal blood flow with venovenous shunting is well documented in cirrhosis; indeed, the direction of flow may even be reversed (hepatofugal blood flow)[30], which may prevent tumour cells ever reaching the liver. However, this would account only for differences with respect to tumours arising in the portal distribution and there is limited support for this hypothesis. In the present analysis the effects of cirrhosis on the development of metastases in general and for tumours within the portal distribution were found to be similar. Also, if the tumour burden were simply being shunted to the next vascular bed, an increase in the proportion of extrahepatic tumours would be expected. Fisher *et al.*[16] searched for this and found the rates of extrahepatic malignancy to be equal in cirrhotics and non-cirrhotics in the absence of liver tumours.

The normal liver sinusoids are lined by fenestrated endothelium and do not have the usual underlying basement membrane[31]. In cirrhosis, the sinusoids undergo a process whereby the endothelial fenestrations are lost and a basement membrane develops, so-called capillarization[32]. This represents an improved physical barrier to tumour cell invasion. Furthermore, there are extensive changes in the adhesion molecules expressed by the hepatic sinusoidal endothelial cells[33,34]. In capillarized sinusoids the adhesion molecule changes include increased expression of platelet-endothelial cell adhesion molecule (PECAM) 1 and the laminin receptors $\alpha_6\beta_1$ and $\alpha_2\beta_1$, and reduced expression of cluster of differentiation (CD) 44[34]. The receptor changes are associated with corresponding changes in the receptor proteins of the extracellular matrix, such as laminin[34]. As adhesion molecules play a pivotal role in metastasis, changes to these ligands may be important, although they are not yet fully understood.

The cytokine microenvironment is changed in response to cirrhosis and varies also according to the underlying cause. For example, high levels of tumour necrosis factor (TNF) α may be detected in the cirrhosis associated with hepatitis C virus infection but not in alcoholic liver cirrhosis[35]. The presence of lymphocytes expressing TNF-α in and around tumours is associated with improved prognosis[36]. The changes in the cytokines modulate a chronic immune response which is ongoing in cirrhosis[37] and which, while causing yet more liver damage, may afford some protection against transformed cells.

During invasion and growth of tumours, various enzymes, including matrix metalloproteinases, break down the extracellular matrix. The cirrhotic liver has been shown to have higher levels than normal of tissue inhibitors of matrix metalloproteinases[38]. This provides a further mechanism by which the incidence of hepatic metastasis may be reduced.

Fisher and Fisher[39] developed an animal model of cirrhosis and metastasis in the rat. They used a fixed dose of carbon tetrachloride to induce liver damage and a sarcoma cell line injected via the portal vein to induce liver metastasis. This model failed to reveal any protective effect of cirrhosis. Indeed, the treated rats developed more advanced disease. The failure of the animal model to support the hypothesis is disappointing, but the methods used are now questionable. For example, an aggressive sarcoma cell line is perhaps not the most representative of common tumours and the method of induction of cirrhosis has now been superseded by more reliable techniques[40].

Conclusion

There is evidence to support the hypothesis that the cirrhotic liver is protected from the development of metastasis. While confounding bias cannot be excluded from the post-mortem evidence, there is additional evidence from clinical and scientific studies that must be taken into account. The findings of this meta-analysis may represent a spurious precision, but many plausible mechanisms exist to explain this interesting phenomenon and further research is warranted. If, indeed, the cirrhotic liver is protected from the spread of secondary cancers, this ‘experiment of nature’ may yield an opportunity to investigate the key steps of the metastatic cascade and allow insight into how future patients might be protected from this malignant process. Finally, it is also important to note that the cirrhotic liver can, and does, suffer from metastatic disease, albeit with a lower frequency than normal liver. Thus the presence of both cirrhosis and a liver mass does not always indicate a primary liver tumour.

Acknowledgements

This work was supported by a grant from the Freeman Hospital Gastrointestinal Research Fund; there are no conflicts of interest.

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Illustrated review of new imaging techniques in the diagnosis of abdominal wall hernias

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Background: The assessment of abdominal wall hernias has long been a clinical skill that only occasionally required the supplementary radiological assistance of herniography. However, with the advent of cross-sectional imaging, a new range of diagnostic tools is now available to help the clinician in difficult cases.
Methods: This review explores the ability of computed tomography and magnetic resonance imaging to demonstrate many of the hernias encountered in the anterior abdominal wall. Also discussed is the role of imaging techniques in the management of a variety of hernias.
Results and conclusion: Cross-sectional imaging techniques are being employed with increasing frequency for the assessment of hernias. Although the anatomical detail can usually be delineated clearly, the accuracy of the various methods and their place in the clinical management of hernias has yet to be fully determined.

Paper accepted 20 May 1999

British Journal of Surgery 1999, **86**, 1243–1249

Introduction

Abdominal wall hernias in their various guises form a commonly encountered group of surgical conditions which range in presentation from asymptomatic to life-threatening emergencies. Radiological imaging is not normally required to assist in the management of hernias; clinical examination usually allows an accurate diagnosis. However, herniography, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are all established and accepted investigations for imaging hernias in cases of diagnostic uncertainty[1–3]. Some reports in the literature, including a number of recent publications, have cast doubt on the ability of imaging techniques (in particular CT and ultrasonography) to assess hernias accurately[4]. Although some of these criticisms may have been valid 10 years ago, the recent improvement in contrast and spatial resolution in cross-sectional imaging has altered this. Numerous publications now attest to the ability of cross-sectional imaging to depict the anatomy of hernias clearly[5–7].

Methods

In this review illustrations are presented of the various abdominal wall hernias that are encountered routinely in clinical practice. In most cases the imaging parameters were chosen to optimize the assessment of some other disease process and the hernias were observed simply as incidental findings. Nevertheless, the depiction of the hernias is clear. When imaging is performed specifically to assess a hernia, techniques can be designed to provide optimal anatomical detail.

Incisional hernia

Hernias resulting from abdominal wall incisions are common. A hernia of some degree occurs during the closure of approximately 10 per cent of all anterior abdominal wall incisions[8]. Such incisional hernias are more common following midline incisions through the relatively avascular linea alba and are relatively less common following transverse incisions, especially where muscle-splitting approaches have been used (e.g. appendicectomy)[9]. Most incisional hernias noted at cross-sectional imaging are incidental findings encountered during radiological examination for unrelated clinical problems. However, the accurate demonstration of the size and site of the hernial orifice, along with the contents of the sac, may be useful in assessing the potential risk of strangulation or the likely success of hernia repair. Imaging is also useful when early dehiscence of the muscle layer in an anterior abdominal wall closure occurs without disruption of the

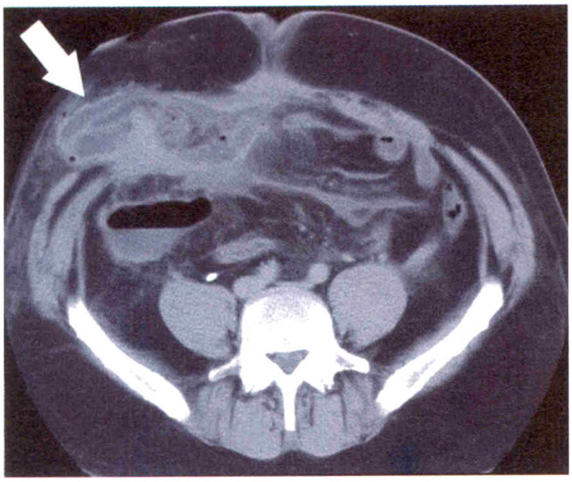

Fig. 1 Axial computed tomogram through the abdomen of a 30-year-old man who presented with small bowel obstruction and a tender red mass at the site of a reversed ileostomy performed 3 days earlier. Loops of distended fluid-filled small bowel (arrow) incarcerated in an ileostomal incisional hernia are demonstrated

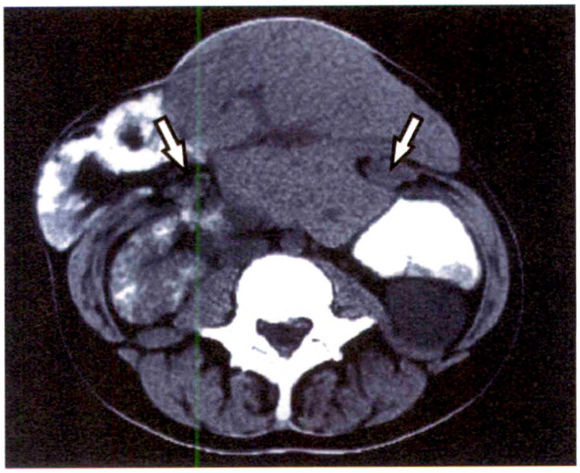

Fig. 3 Axial computed tomogram of the upper abdomen of a 24-year-old woman with a persistent anterior abdominal wall defect despite repeated plastic procedures. Small bowel and liver have herniated between hypoplastic rectus abdominis muscles (arrows)

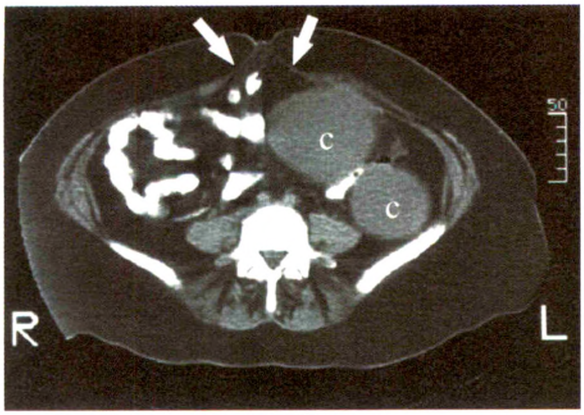

Fig. 2 Axial abdominal computed tomogram of a relatively obese 72-year-old woman with slowly enlarging mesenteric cysts (c). The umbilical cicatrix (arrows) has been recanalized by the chronically raised intra-abdominal pressure, forming a true umbilical hernia

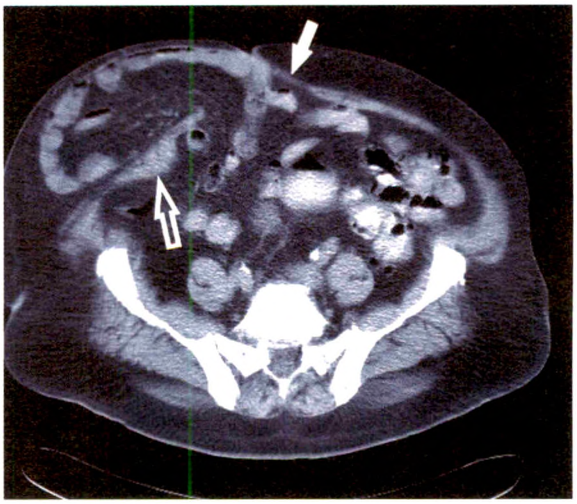

Fig. 4 Axial abdominal computed tomogram at the level of the umbilicus of a 68-year-old man. A large paraumbilical hernia containing small bowel is demonstrated lying to the right of an intact umbilical cicatrix (solid arrow). The right rectus abdominis is displaced laterally (open arrow)

overlying skin[10]. In such cases differentiation between an incarcerated hernia and a postoperative haematoma may be difficult (*Fig. 1*).

Umbilical hernia

Umbilical hernia is commonly encountered in children and the elderly[11]. Anatomically it is divided into 'true' umbilical and paraumbilical hernia. This distinction, although not crucial in the surgical repair of the hernia, provides an indication of the aetiology and can be clearly demonstrated by CT. Classically 'true' umbilical hernias are found in children or in adults with conditions that produce a chronic increase in intra-abdominal pressure (ascites, polycystic renal disease, ovarian cysts). These represent either a failure of closure of the vitellointestinal duct in congenital cases, or the reopening of the tubular scar that the duct forms at the umbilicus (*Fig. 2*). Failure of closure of the vitellointestinal duct combined with failure of the gut to return to the abdominal cavity during intrauterine life results in exomphalos (*Fig. 3*). Paraumbilical hernia, on the other hand,

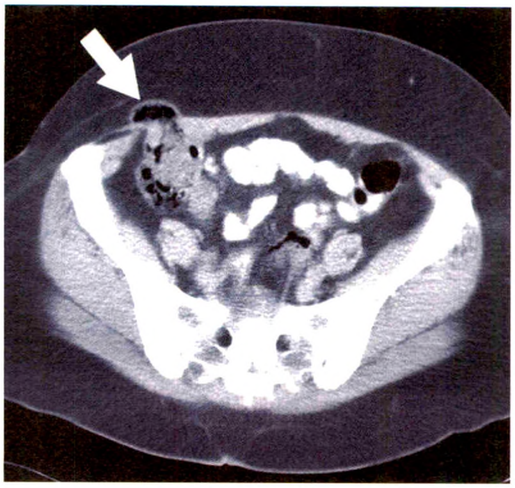

Fig. 5 Axial abdominal computed tomogram of a 63-year-old woman revealing an asymptomatic Spigelian hernia (arrow)

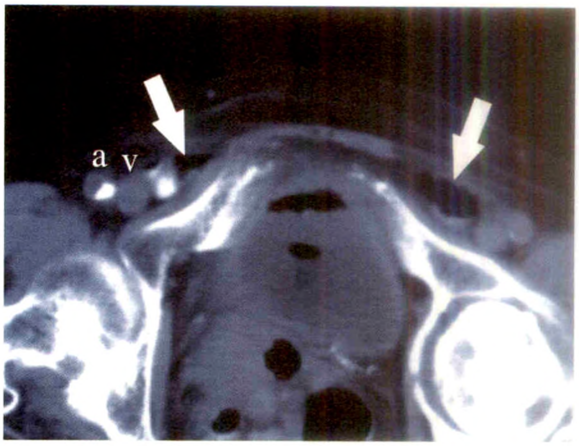

Fig. 7 Axial pelvic computed tomogram of an 82-year-old woman with bilateral femoral hernia. Small bowel loops (arrows) can be identified in the femoral canal medial to the femoral artery (a) and vein (v), and lateral to the pubic symphysis

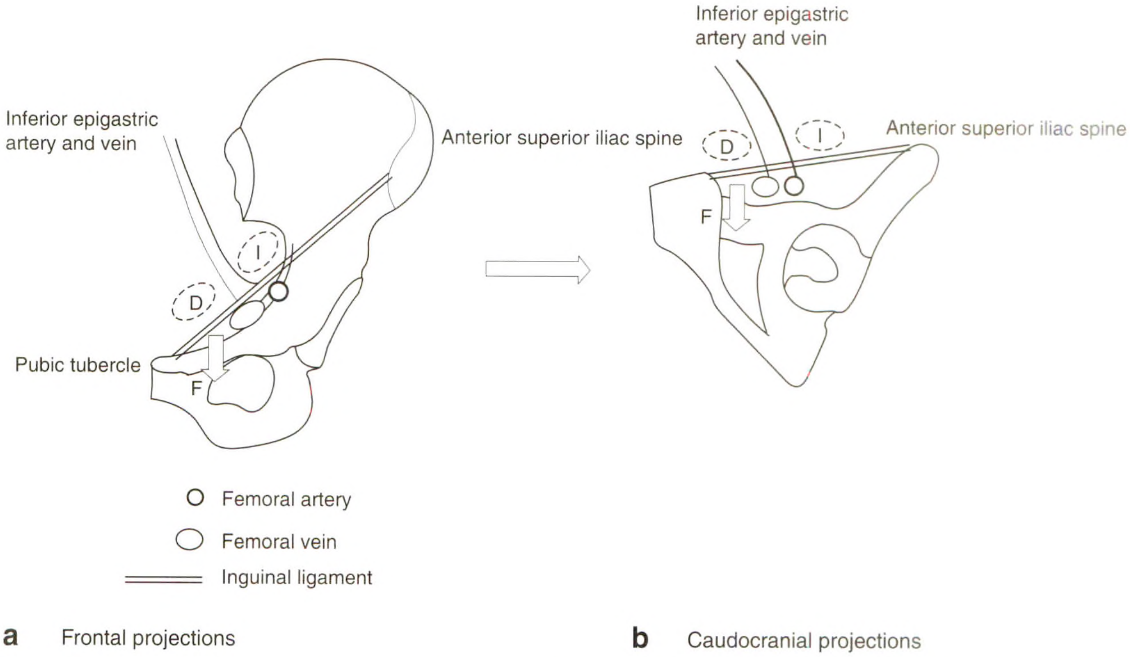
Inferior epigastric artery and vein
Anterior superior iliac spine
I
D
Pubic tubercle
F
Inferior epigastric artery and vein
D
I
Anterior superior iliac spine
F
Femoral artery
Femoral vein
Inguinal ligament
a
Frontal projections
b
Caudocranial projections

Fig. 6 Schematic representation of the left hemipelvis. The relationship between inguinal and femoral hernias is depicted in **a** frontal and **b** caudocranial projections. D, Direct inguinal hernial neck; F, femoral hernial neck; I, indirect inguinal hernial neck

tends to occur in the elderly patient in whom there is connective tissue degeneration and in patients with respiratory disorders causing a chronic cough (*Fig. 4*).

Spigelian hernia

Spigelian hernia is a protrusion of intra-abdominal fat or bowel through a defect in the 'Spigelian aponeurosis' (*Fig. 5*). This is the part of the anterior abdominal wall aponeurosis that lies between the linea semilunaris laterally and the lateral edge of the rectus musculature medially. A Spigelian hernia is classically found at a position cranial to the junction of the inferior epigastric vessels and the Spigelian aponeurosis. Caudal to this point it is termed a 'low Spigelian hernia'[12]. Spigelian hernia is uncommon and is often asymptomatic; patients tend to be obese. Making a firm diagnosis on clinical examination in the obese patient may be difficult; this may result in surgical exploration of the anterior abdominal wall being undertaken on the basis of suspicion raised by the history alone and not necessarily firmly established by preoperative clinical examination. Both ultrasonography and CT can elegantly demonstrate a Spigelian hernia before operation[13–16]. It is also important to note that omentum within such a hernia may infarct and cause symptoms[17]. Radiologists may falsely assume that a hernia containing fat alone is unlikely to cause symptoms.

Inguinal and femoral hernias

The anatomy of hernias in the groin is well described in standard surgical textbooks[18]. Differentiation between the different types of hernia at this site, based on clinical signs using key anatomical landmarks, is a basic part of undergraduate medical and postgraduate surgical training. However, even experienced consultant surgeons cannot always differentiate accurately between indirect and direct inguinal hernia, especially in the obese[19,20]. The key to interpreting cross-sectional images of hernias in the groin is, not surprisingly, to translate the traditional frontal schematic diagrams of surgical landmarks into the plane of the image (*Fig. 6*). With CT this is most commonly in the axial plane. Femoral hernias can be differentiated from inguinal hernias by their medial position within the femoral canal posterior to the line of the inguinal ligament (*Fig. 7*). The neck of an indirect inguinal hernia can be demonstrated at the deep inguinal ring lateral to the inferior epigastric vessels (*Figs 8* and *9*) whereas direct inguinal hernias remain medial to the inferior epigastric vessels throughout. Spiral CT protocols commonly used for abdominal imaging (e.g. 10-mm slice thickness, a pitch of 1, with images recon-

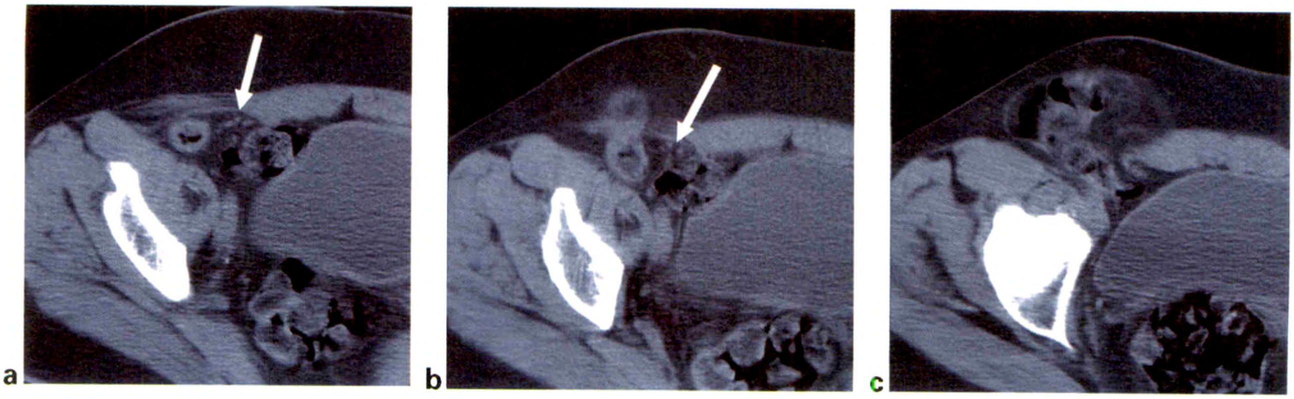

Fig. 8 10-mm axial spiral computed tomographic sections through the right deep inguinal ring. An indirect inguinal hernia containing sigmoid colon is demonstrated entering the inguinal canal lateral to the inferior epigastric vessels (arrow)

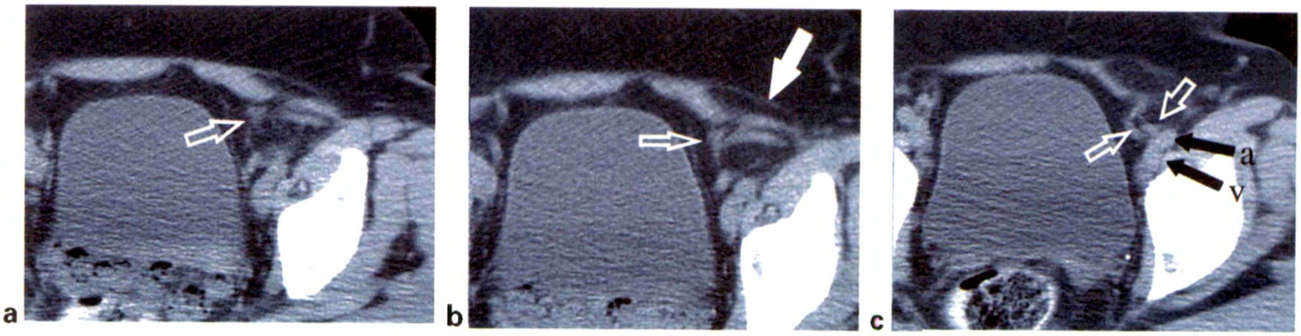

Fig. 9 5-mm axial spiral computed tomographic sections through the left deep inguinal ring of a 53-year-old obese woman who presented with a tender lump in the mons pubis.
b The contents of the indirect hernial sac (fat and vessels consistent with omentum; solid arrow) can be seen entering the deep inguinal canal lateral to the inferior epigastric vessels (open arrows).
c The inferior epigastric vessels are clearly depicted arising from the external iliac artery (a) and vein (v)

structed every 10 mm) will usually demonstrate the inferior epigastric vessels (*Fig. 8*). Dedicated protocols using thinner slice collimation (e.g. 5 mm), with more frequent reconstructions, will demonstrate these vessels in virtually every patient (*Fig. 9*).

Indications for imaging

Herniography (contrast peritoneography) was first described in 1967 for use in the detection of contralateral hernias in children[21]. However, the most common indica-

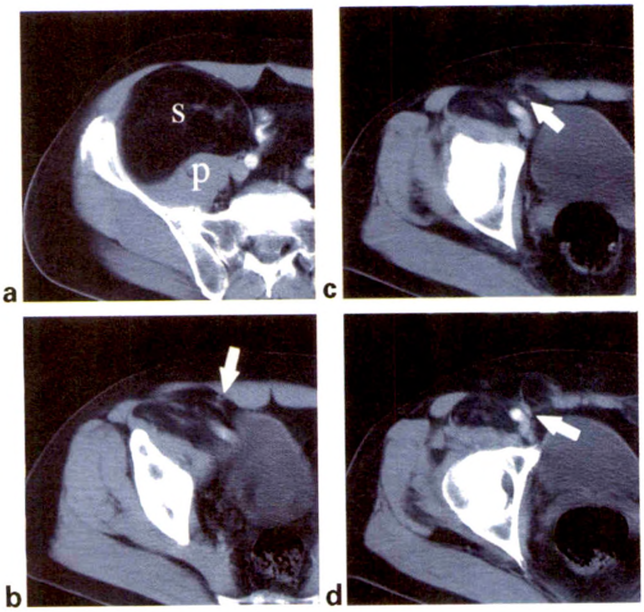

Fig. 10 10-millimetre spiral computed tomographic images through the lower abdomen and right groin of a 57-year-old man presenting with an apparent right inguinal hernia. The images depict a liposarcoma (s) arising from the retroperitoneum alongside the right psoas (p) and extending into the right groin on either side of the inferior epigastric vessels (arrow), mimicking a 'pantaloon' hernia

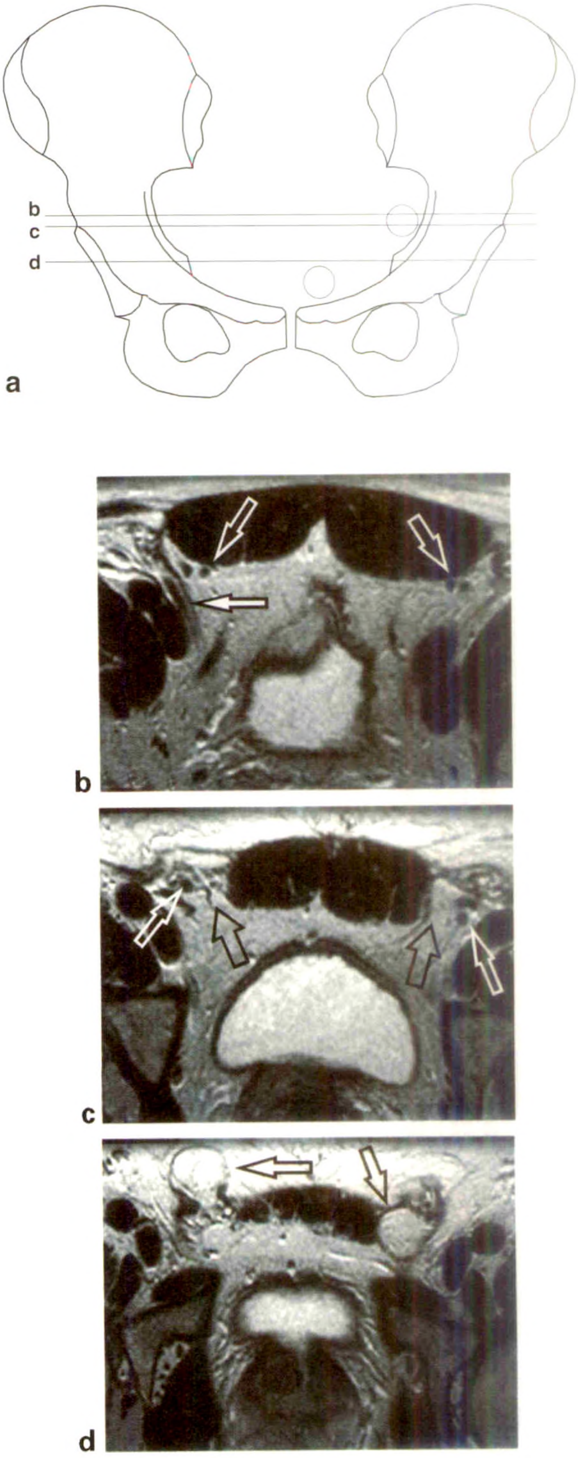

Fig. 11 T1-weighted axial magnetic resonance (MR) imaging performed to stage prostatic carcinoma in a 61-year-old man.
a Diagrammatic representation of the pelvis demonstrating the position of the axial planes of the following MR images. **b** and **c** are at the level of the deep inguinal ring (circle) and **d** is at the midpoint of the inguinal canal.
b Note the vas deferens and testicular vessels (solid white arrow) medial to the external iliac vessels. Inferior epigastric vessels (open white arrows) are posterolateral to the rectus abdominis muscles.
c Open black arrows point to the fat entering the origin of the direct inguinal hernias medial to the inferior epigastric vessels (open white arrows).
d Open black arrows point to direct inguinal hernias containing fat. The defect in the posterior wall of the inguinal canal is clearly seen on the right

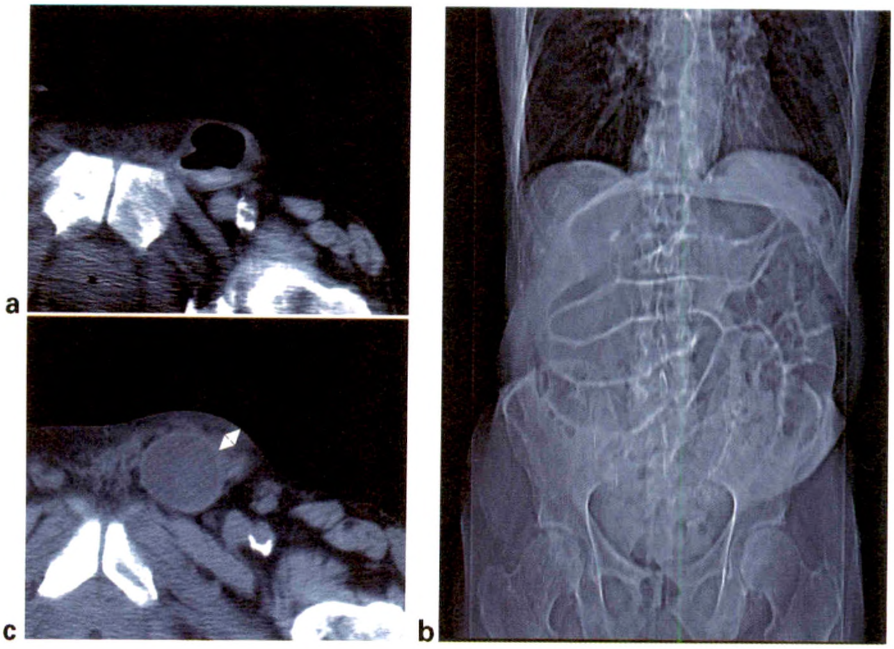

Fig. 12

a Left inguinal hernia noted incidentally during abdominal computed tomography (CT) in a 73-year-old man.

b CT projection radiograph performed during an emergency admission 6 months later. Multiple dilated small bowel loops indicate small bowel obstruction.

c Axial CT through the left groin reveals a distended thick-walled loop of small bowel in the inguinal canal with oedema of the overlying skin and subcutaneous tissue (arrow). At operation an incarcerated left inguinal hernia was confirmed as the cause of obstruction, and repaired

tion is in the investigation of patients with groin pain in whom an occult hernia is suspected[22–24]. Herniography detects hernias in 36–54 per cent of this group of patients. The false-positive rate varies between 0 and 18·7 per cent and the false-negative rate between 2 and 7·9 per cent[22,23]. False-negative findings are thought to be due mostly to fat plugging the hernial orifice.

Cross-sectional imaging techniques are being used increasingly to detect occult hernia. However, their efficacy has not been well assessed. The sensitivity of CT in detecting abdominal wall hernias has been reported as 83 per cent with a specificity of between 67 and 83 per cent[25]. False-negative results may be attributed to reduction of the hernia with the patient in the supine position. Some authors stress the importance of performing a Valsalva manoeuvre during the examination[25].

Distinguishing between abdominal wall disruption and haematoma or infection in the early postoperative period may be difficult. Cross-sectional imaging with ultrasonography or CT is the most appropriate technique at this stage (*Fig. 1*). Occult recurrent or incisional hernias may be assessed by either cross-sectional imaging or herniography, depending on local availability. Cross-sectional imaging, in particular CT, is useful when there is suspicion that another disease process is either mimicking or precipitating a hernia (*Fig. 10*).

Discussion

The advent of MRI has extended the list of imaging techniques available for assessing hernias[26,27] (*Fig. 11*). Herniography has a low complication rate, relating mainly to accidental colonic puncture, of less than 1 per cent[28]. However, it is invasive and is likely to be replaced by cross-sectional imaging. Ultrasonography, CT and MRI are appropriate investigations for demonstrating an acutely strangulated hernia in the obese and in problem cases where there is diagnostic uncertainty following physical examination (*Fig. 12*). However, when a patient presents non-urgently with a history suggesting a reducible hernia (which cannot be confirmed by clinical examination), ultrasonography and herniography are the appropriate investigations[29]. They have the advantage of being real-time examinations which allow the patient to stand upright and perform a Valsalva manoeuvre to demonstrate the hernia to best advantage. The ability to distinguish direct from indirect inguinal hernia accurately with CT or MRI may be useful in identifying a group of patients at high anaesthetic risk with reducible direct hernias in whom surgery may not be mandatory[30]. In the future, increased availability of MRI systems with rapid data acquisition may allow the dynamic evaluation of a hernia in multiple imaging planes[26].

Acknowledgements

The authors thank the late Dr Barry Jones, consultant radiologist, Peterborough District Hospital, for the loan of several of the illustrations.

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Professor Denis Castaing, Editor of *Annales de Chirurgie*, has selected the best from Issues 8, 9 and 10 of 1998. A reciprocal digest written by our European Editor, Mr Colin Johnson, is published in the French journal. The digest for issues 8, 9 and 10 of 1998 covers several aspects of general surgery including appendicitis, spleen, colorectal and neck surgery.

Appendicectomy

In the first paper[1] 200 records of patients undergoing appendicectomy in an emergency surgery department between January 1993 and August 1994 were submitted to a retrospective and descriptive study with evaluation of the medical file content. Data collection rates were lower than expected, particularly for the association of temperature, abdominal tenderness and white blood cell count, which was found in only 159 (81 per cent) of 197 records. Data were collected less often for women, for patients undergoing laparoscopic operation and when histopathological review showed the absence of acute inflammation. The rate of acute appendicitis was 74 per cent (145 of 197). The rate of appendicectomy without acute inflammation was higher in women (37 (35 per cent) of 107) than in men (15 (17 per cent) of 90), and higher in patients who underwent laparoscopic appendicectomy (33 (43 per cent) of 77) than in those who had laparotomy (19 (16 per cent) of 119). These results highlight the need to improve completion of medical records with better collection of clinical data, which could lead to improved quality of care and management of appendicitis-like syndromes, which is the first step to a reduction in the number of appendicectomies.

To evaluate the impact of laparoscopic appendicectomy on the incidence of unnecessary appendicectomy (histologically normal appendices), Barrat *et al.*[2] from Bondy, France, designed a retrospective study of 1220 consecutive appendicectomies (carried out over 10 years). There were 841 women (69 per cent) and 379 men with a mean age of 23·5 (17–73) years. Indication for operation was the presence of at least one of the following three criteria: right iliac fossa guarding, fever greater than 38°C and hyperleucocytosis greater than 10 000 cells/mm^3. Patients were divided into two groups: the 930 patients in group I were operated on by laparotomy and group II, comprising 355 patients, underwent laparoscopic exploration with appendicectomy when macroscopic abnormalities were observed (290 cases). In group I, the incidence of histologically normal appendix was 25 per cent. In group II, the incidence was only 8 per cent ($P = 0{\cdot}015$). In 65 cases (18 per cent), a macroscopically normal appendix was left in place; in 55 patients the symptoms were due to another identified cause; however, in ten cases no cause was found. This study suggests that laparoscopy significantly reduces the number of histologically normal appendices resected because another cause is identified more easily. This approach reduces costs without having any adverse consequences on outcome.

One-third of all patients with abdominal pain and one-quarter of those with right iliac fossa pain admitted urgently to hospital leave hospital with no precise diagnosis. From a prospective series of 400 patients hospitalized for right iliac fossa pain in two Swiss cantons, Groebli *et al.*[3] assessed the medium-term outcome of 107 patients (30 per cent) with no identified aetiology with or without surgical exploration. Forty patients were lost to follow-up; 67 cases were reviewed at 5 years. No major diagnosis was missed. Over this 5-year period 30 patients (45 per cent) experienced a further episode of abdominal pain. Of 21 patients reviewed for another episode of right iliac fossa pain, seven were readmitted to hospital; five appendicectomies were performed, with three showing histologically confirmed acute appendicitis (4 per cent of the series). There was no significant evidence to suggest a psychological component in the recurrent nature of the pain. The authors concluded that the patient and their attending physician must be informed of the non-specific diagnosis established during the first period of hospitalization. Cancer must be excluded formally in patients aged over 50 years.

Spleen surgery

As operative bleeding is the main complication and main cause of conversion to open surgery during laparoscopic splenectomy, Gossot[4] presents the advantages of the posterior approach to the splenic vessels. In 24 patients, a posterior approach to the splenic vessels was used with the patient in the full lateral position. Division of short gastric vessels and lower pole vessels was performed with ultrasonography. The main vascular pedicle was stapled. The spleen was removed through a Pfannenstiel incision. There were 11 men and 13 women with a mean age of 38 (range 17–71) years. Sixteen patients had immune thrombocytopenic purpura, two had human immunodeficiency virus-related purpura, three had haemolytic anaemia and two had spherocytosis. There was no conversion to laparotomy. The mean splenic weight was 372 (range 162–1420) g. In all but one patient, intraoperative blood loss was less than 60 ml, and was zero in seven patients. The mean operating time was 126 (range 70–220) min, including the time required for change of position and Pfannenstiel incision. There was no death. One patient developed pancreatitis. In patients with an uncomplicated course, the mean postoperative stay was 4·1 (range 2–8) days. The author's conclusion was that lateral position with a posterior approach to splenic vessels allows for safe vascular control.

To determine the value of a computed tomography (CT) scoring system in the choice of non-operative treatment *versus* surgical management for splenic trauma, Froment *et al.*[5] collected retrospectively the data from 62 adults with isolated blunt splenic trauma. Some 22 patients (35 per cent) without haemodynamic instability presenting with pain localized in the left flank were primarily managed conservatively; three subsequently required splenectomy. Forty patients (65 per cent) were operated on immediately, 32 because of clinical criteria and eight on the basis of laboratory criteria. Forty-five patients with no initial haemodynamic disorders were investigated by abdominal CT. Splenic injuries were classified retrospectively according to the Resciniti CT scoring system. All 13 patients with a splenic injury score over 5·5 underwent operation, 11 early and two after failure of conservative management. The authors considered a score of 5·5 or greater, which included 21 per cent of their patients, to be an indication for surgery; in this case, a conservative approach should not be attempted, even in the absence of immediate clinical and laboratory operative criteria.

The conservative management of blunt splenic trauma is accepted more in children than in adults, in order to avoid serious postsplenectomy infectious complications. To evaluate the results of conservative management, a retrospective study (between 1 January 1991 and 31 December 1995) of 21 children was undertaken by Varlet *et al.*[6]. Eleven cases were identified, and ten were associated with other visceral, musculoskeletal or head injuries. The lesion was subcapsular or intraparenchymal haematoma in eight patients and ruptured spleen in 13. All the children were initially managed conservatively, except in the presence of unstable haemodynamic parameters following resuscitation, perforated bowel or secondary complication. An emergency operation for splenic trauma was never required over this 5-year period. Four children required secondary surgery, two for left renal lesion, one for pancreatic pseudocyst and one for epidermoid cyst of the spleen discovered incidentally at the time of the trauma (partial splenectomy). No immediate or long-term complications were observed with a mean follow-up of 6 months. The conclusion was that conservative management of blunt splenic trauma with a very low blood transfusion rate is possible, and total splenectomy was never required.

Colorectal surgery

To assess the technical and functional results of total anorectal reconstruction with double dynamic graciloplasty after abdominoperineal resection, Rullier *et al.*[7] reviewed ten patients operated on for low rectal adenocarcinoma between May 1995 and December 1996. There were six men and four women, with a mean age of 54 (range 39–74) years. All patients had preoperative radiotherapy and six had postoperative chemotherapy. The surgical procedure was performed in three stages: first anoperineal resection, coloperineal anastomosis, double graciloplasty and ileostomy; second, 3 months later, implantation of stimulator and intramuscular leads; third, after a 2-month training period, the stoma was closed. There was no operative death. Early and late complications occurred in five patients: two colonic fistulas, one necrotic colon, one prolapsed ileostomy, one neosphincter stenosis, and one sepsis of the stimulator. No patient had recurrence of the disease (mean follow-up 16 months), but two died at 3 and 8 months from anorexia and pulmonary embolism respectively. Seven patients had functional evaluation 1 year after stoma closure: six were continent (five with spontaneous defaecation, one with enemas) and one was incontinent. The authors concluded that anorectal reconstruction with dynamic graciloplasty may be an alternative to permanent colostomy for selected patients after abdominoperineal resection, but there is a high morbidity rate and the quality of life must be evaluated.

Adjuvant chemotherapy for colonic and rectal cancers may improve survival but incur expense, inconvenience, discomfort and risk of complications. To evaluate these quality-of-life issues, Bellemare *et al.*[8] designed a study with two clinimetric scales for quality-of-life measurement. The seven selected criteria considered most important were determined by interviewing treated patients, who reported problems such as nausea and vomiting, diarrhoea, perineal dermatitis, asthenia, impairment of daily activity, family support, and difficulties of daily transportation to hospital. This study revealed a diminished quality of life for both patients with colonic cancer (7 on a scale of 10) and for those with rectal cancer (6 on the same scale). The effect of radiotherapy seems to be responsible for this difference. This study is one of the first to approach quality of life from the point of view of the patient.

Surgery of the neck

A study to assess the feasibility of a minimally invasive parathyroidectomy performed by videocervicoscopy included 19 patients operated on for hyperparathyroidism[9]. Preoperative localization by ultrasonography and/or technetium-99m sestamibi scan was performed in 17 patients.

Initially the authors used three 2·5-mm cannulas and a 2·5-mm endoscope. This technique failed in the first two cases because of lack of optical clarity of the 2·5-mm endoscope. A 5-mm endoscope was used subsequently. Carbon dioxide insuflation was maintained at 10 mmHg with a low flow rate of 3 l/min. Three cannulas were inserted into the cervical space: one of 5 mm for the endoscope, and two 3-mm cannulas for instruments. A unilateral neck exploration was carried out in five cases and a bilateral neck exploration in 14. Enlarged glands were discovered in 13 patients (12 adenomas, one hyperplasia of the four glands). Eight adenomas were removed via a short midline incision, and four others via a short lateral incision. Horizontal cervicotomy was required in seven cases (four failures to identify the abnormal gland, one for thyroid cancer discovered incidentally, one for hyperplasia of the four glands and one for anterior jugular vein bleeding). Except for this case of bleeding, no other complication occurred. Subcutaneous emphysema resorbed in 3 h. All patients were discharged within 48 h, two within 24 h. Two months after operation 18 patients had normal serum calcium levels. This study demonstrates that videocervicoscopy is safe and feasible in patients with primary hyperparathyroidism.

Second procedures for recurrent thyroid disease are known to carry a high risk of iatrogenic damage, particularly to the inferior laryngeal nerves and parathyroid glands. This risk has been clearly evaluated for the primary procedure, but less so for second procedures. A series of 117 patients with solitary or multiple cold thyroid nodules was evaluated[10]. The level of transient and permanent recurrent laryngeal nerve palsy was 2·6 and 1·7 per cent respectively. The level of transient and permanent hypocalcaemia was 12·9 and 4·6 per cent respectively. The frequency of reoperation for recurrent disease involving the pyramidal lobe following total thyroidectomy (six of 117 patients) highlights the importance of removing it during the primary procedure. The number of cases of cancer discovered at reoperation was five (4·3 per cent) of 117.

Reconstruction of the oropharynx and hypopharynx is difficult because of their wide diameter. Germain *et al.*[11] reported on seven patients who underwent reconstruction with a free U-shaped jejunal transplant after circular pharyngolaryngectomy for hypopharyngeal cancer invading the oropharynx (T4). There was no operative death and no fistula. One stenosis of the distal anastomosis was treated by pneumatic dilatation. All the patients had postoperative radiotherapy. Four patients were alive without recurrence at 3, 2, 2 and 1 years. One patient was alive with recurrence at 1 year. Two patients died from recurrence at 4 and 3 years. The authors conclude that this transplant allowed reconstruction of the upper digestive tract after wide resection of the pharynx.

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Digest

For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the January to March 1999 issues of *Der Chirurg*. A digest of the *BJS* for the same period, written by Mr Colin Johnson, appears in the German journal. The 14 leading articles of the year's first quarter focus on the cooperation between surgeons and anaesthetists on the diagnosis and treatment of liver metastases[1–5].

Liver resection at the drawing board

Although up to 80 per cent of healthy liver tissue may be removed without critically compromising liver function, the determination of proper resection planes in large or centrally located primary tumours or liver metastases may prove difficult. This problem becomes particularly evident in patients with compromised liver function due to coexisting liver disease. The surgeon has to form a virtual three-dimensional picture of the tumour in relation to major portal or hepatic venous vessels based on information provided by two-dimensional computed tomography scans or nuclear magnetic resonance images and estimate how much functioning liver parenchyma will be lost, if the tumour is removed with adequate margins. This also requires an estimation of the volume of liver parenchyma dependent on vasculature that will be sacrificed in order to perform a potentially curative liver resection.

A group from Heidelberg[6] has aimed to establish a computer-assisted three-dimensional volumetric operation planning system for liver resection. Using data from routine helical computed tomography scans, three subclasses of liver parenchyma, hepatic vessels and tumour tissue were segmented semiautomatically. A dedicated segmenting tool was established using region growing algorithms in combination with an 'intelligent' border finder. Visualization is performed by the 'Heidelberg ray tracer' and vascular trees are visualized as three-dimensional graphs. Factitious pseudoconnections between hepatic venous and portal vessels are separated automatically. Safety margins can be programmed and automatically incorporated into the proposed resection planes developed by the system, which also takes into account the amount of liver parenchyma dependent on blood vessels that have to be removed. The system thus offers an individualized proposal for resection. Using this approach, considerable variation of individual segmental anatomy from Couinaud's anatomical segmentation of the liver has been observed. The authors conclude that a combination of virtual reality with artificial intelligence allows calculation of complete resection protocols, making liver resection a more objective procedure. In cases of difficult tumour location, various alternative resectional concepts can be tested beforehand. They expect therefore that virtual reality in liver surgery will improve teaching, surgical training and operative planning.

Hartmann's procedure

Colostomy and closure of the rectal stump is an approved method in emergency colon surgery. It has been criticized in the past because a second procedure is required to restore bowel continuity and because the colostomy is never taken down in some patients. Surgeons from Vienna[7] have now looked at the problem again and reported the long-term outcome of patients who have undergone Hartmann's procedure subsequent to colonic perforation.

Between 1982 and 1997 a total of 230 patients were operated for colonic perforation. Hartmann's procedure was performed in 103 patients. Median age of the 52 men and 51 women was 69 years. Indications for discontinuous resection were severe peritonitis, poor general condition of the patient and a high risk of anastomotic leakage. Peritonitis was staged according to Hinchey. Twenty-four patients had stage 2, 55 had stage 3 and 24 patients had stage 4 peritonitis. Peritonitis was caused by a perforated diverticulum ($n = 65$), inflammatory bowel disease ($n = 7$), necrotizing pancreatitis ($n = 15$), malignant disease ($n = 15$) or various other conditions ($n = 9$). Seventeen patients died after operation and in ten patients the primary cause of death was peritonitis. Mean time in hospital was 18 days for 86 surviving patients. After a mean of 122 days continuity was restored in 69 patients (80 per cent). In 34 patients a stapled anastomosis and in 35 a hand-sutured anastomosis was performed. Four patients (6 per cent) had clinical signs of anastomotic leakage. No patient died after restoration of bowel continuity. Mean hospital stay for the second operation was 14 days.

Follow-up information could be obtained for 83 (97 per cent) of 86 patients surviving the initial treatment which included Hartmann's procedure. The median follow-up time from restoration of continuity was 75 months. Restoration of continuity was accomplished in 69 patients (80 per cent). Two patients died before a planned second operation, in three the risk of another operation was considered too high to be justified, five refused another operation and in seven patients anal incontinence precluded restoration of bowel continuity.

After restoration of bowel continuity 53 of 60 patients described their quality of life as good or very good, 12 reported reduced general activity and six patients noted a severe restriction of physical ability. Four patients reported that they had to change their housing and five reported depression. Of patients with a permanent colostomy, nine of 12 considered their quality of life to be good or very good, four observed reduced general activity and two experienced severe restriction of their physical ability. Two patients changed housing because of the colostomy and depression was recorded in two. Differences between the two groups were slight and were not statistically significant. However, patients with a permanent colostomy were significantly older (73 years) than those with restored bowel continuity (59 years) ($P = 0{\cdot}02$, Wilcoxon test).

This report documents that Hartmann's operation is a perfectly acceptable solution for patients with severe peritonitis and it consequently emphasizes that patients must be selected for a primary anastomosis with the greatest of care. The good results after Hartmann's operation, in terms of restoration rates, risk of bowel restoration and quality of life, would make any complication arising from a primary anastomosis performed in the presence of peritonitis hard to accept.

Intraoperative laparoscopy in patients with paediatric hernia

Approximately 50 per cent of children with a unilateral inguinal hernia have a patent contralateral processus vaginalis. One-half of these children will develop an inguinal hernia in the future. The management of these children is still subject to controversy. Authors from Ulm[8] have studied the use of an intraoperative 'no puncture' laparoscopy technique through the open peritoneal sac in children undergoing conventional hernia repair. Between April 1996 and May 1998 a total of 112 children aged 6 months to 7 years undergoing conventional repair of inguinal hernia had intraoperative 'transhernial' laparoscopy. A 5-mm laparoscope with either 30° or 70° view was used. In the case of a wide open contralateral internal inguinal ring (Chin type III) the groin was explored surgically. A total of 19 patients (17 per cent) fulfilled the laparoscopic criteria of a type III internal ring. This was confirmed by open exploration of the contralateral groin and the processus was closed in all 19 patients. Fourteen of these patients were younger than 2 years. The median duration of laparoscopy was 6 (range 3–11) min and no laparoscopy-associated complications were recorded. The authors conclude that intraoperative laparoscopy during planned unilateral inguinal hernia repair in children identifies a substantial number of patients with an open contralateral processus vaginalis and allows simultaneous closure. Routine application of intraoperative laparoscopy may avoid a second period of hospitalization and operation as well as unnecessary routine open bilateral exploration. The method also proved helpful for inspection of incarcerated bowel after repositioning.

Thoracic surgery

Spontaneous pneumothorax predominantly affects younger patients. Traditionally, the first episode of spontaneous pneumothorax is treated conservatively, while surgical treatment is reserved for recurrent pneumothorax. The wider use of video-assisted thoracoscopic surgery (VATS) may lead to a change in this approach. Between October 1995 and December 1997 a total of 28 patients with spontaneous primary pneumothorax were treated at Kiel City Hospital[9]. Two patients responded to conservative treatment with thoracic drainage alone. Twenty-six patients underwent VATS after a mean of 6·7 (range 4–10) days of conservative treatment. In Vanderschueren stage I or II the pulmonary apex was resected and in Vanderschueren stage III or IV the bulla was resected with endoscopic staplers. After operation all patients received intrapleural tetracycline 500 mg and a 28-Fr thoracic drain was inserted, which was removed when the drainage volume fell below 100 ml per day. The mean operative time was 60 (range 34–115) min and a mean of three (range two to seven) stapler magazines was required for resection. Postoperative complications included contralateral pneumothorax in one patient and persistent fistula (three), but no patient died. One patient required bilateral thoracotomy for persistent fistulas from bilateral bullas. Postoperative hospital stay was 6·1 (range 2–29) days. This compares favourably with a retrospectively examined control group of 59 patients undergoing strictly conservative treatment, which required a mean of 10·4 days of hospital treatment. All patients were seen after 3 months and yearly thereafter for a mean follow-up of 19 months. To date no recurrence of pneumothorax has been observed. The authors conclude that VATS allows effective treatment of spontaneous primary pneumothorax and may safely be performed by general surgeons.

Billing, although not immediately treatment related, nevertheless is an important aspect of medical service. Limited financial resources for medical services have led to new reimbursement schemes including fixed rates for specific services. Lang *et al.*[10], from Ulm, have performed a cost analysis of thoracic surgical procedures performed between March and October 1997. The cost of hospital staff, equipment and operating theatre supplies was analysed prospectively for 30 patients undergoing five different types of operation. Resection of more than three pulmonary wedges ($n = 8$), lobectomy ($n = 8$), pneumonectomy ($n = 5$), thoracoscopic wedge resection ($n = 6$) and resection of mediastinal tumour (*n* = 3) were evaluated. The cost of lobectomy was calculated as DM 9927, of pneumonectomy DM 11 562, of thoracoscopic wedge resection DM 12 477 and of mediastinal tumour resection as DM 7532. This was between DM 1907 and 5539 higher than the fixed reimbursement rates for these procedures. Only for multiple wedge resection was the fixed reimbursement rate of DM 866 higher than the calculated cost of DM 6922. In a review of the literature the authors document remarkable differences in procedure-related costs ranging from DM 2290 to 12 500 for multiple wedge resection and from DM 2194 to 12 900 for video-assisted thoracoscopic atypical pulmonary resection.

Despite the important role of lymph node metastases in prognostic staging of non-small cell lung cancer (NSCLC) no standards exist to determine the quality of mediastinal lymphadenectomy. Conversely, researchers from various institutions are unconvinced of the value of radical ipsilateral lymphadenectomy. To determine the correlation between primary tumour location and lymph node metastasis, authors from Munich[11] studied prospectively 270 consecutive patients who underwent complete ipsilateral lymphadenectomy for NSCLC. Patients were classified Union Internacional Contra la Cancrum 1987 stage I (*n* = 115), stage II (*n* = 42) or stage IIIa (*n* = 113). In patients with N_1 positive nodes the 5-year survival rate was higher for those with intrapulmonary positive nodes (39 per cent) than for patients with infiltration of hilar nodes (21 per cent). Skip metastases were demonstrable in up to 81 per cent of patients with N_2 disease. The authors conclude that primary tumour location does not predict the location of lymph node metastases and, owing to the variability of lymph node metastases and the frequent presence of skip metastases, systematic radical ipsilateral lymphadenectomy should be performed.

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Association of Surgeons of Great Britain and Ireland

The Annual Scientific Meeting of the Association of Surgeons of Great Britain and Ireland was held in Brighton on 5–7 May 1999 under the Presidency of Professor R. C. N. Williamson. The abstracts of the oral and poster presentations of the original work presented at the meeting have been published in a BJS Supplement that accompanied the June 1999 issue of the Journal. The articles that follow in the present issue describe work presented at the Brighton meeting that have been accepted for publication after peer review by the Journal's referees. Other papers from this meeting will appear in subsequent issues.

Partial ileal resection for hypercholesterolaemia in patients undergoing surgery for obesity

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Paper accepted 20 June 1999

Introduction

Hypercholesterolaemia is a major risk factor for coronary heart disease (CHD) and lowering plasma cholesterol levels by diet, statins or ileal bypass reduces the incidence of coronary events. The main approach should be medical, by diet and drugs. In morbidly obese patients who are undergoing bariatric surgery, bypass of the distal small bowel, as pioneered by Buchwald *et al.*[1], lowers plasma cholesterol levels and protects against CHD. Similar reductions in cholesterol concentration might be achieved, but with less troublesome side-effects, if a limited ileal resection were carried out, proximal to the ileocaecal sphincter.

This paper reports preliminary results of partial ileal resection (PIR) combined with a gastric restrictive procedure, the Magenstrasse and Mill (M and M) operation[2], for the treatment of patients with both morbid obesity and hyperlipidaemia.

Patients and methods

The study included six patients (five women; aged 25–55 years) who presented with both morbid obesity (body mass index greater than 40 kg/m^2) and hypercholesterolaemia (fasting cholesterol level above 5·8 mmol/l). Each patient underwent an M and M procedure combined with PIR. Five matched obese patients with hypercholesterolaemia (four women; aged 28–50 years) who had a M and M operation alone were studied for comparison (*Table 1*). All patients were seen 1 year after operation, when measurements of body mass index and fasting lipids were repeated.

The M and M procedure is illustrated in *Fig. 1*. The stomach was divided vertically by stapling instruments from incisura to cardia and the staple lines inverted. The narrow

Table 1 Effects of the Magenstrasse and Mill procedure with and without partial ileal resection on plasma lipids and body-weight

	Before operation	After operation	Change (%)	P*
Total cholesterol (mmol/l)				
M and M + PIR	7·2(1·3)	5·4(0·8)	−23·8	0·03
M and M	6·8(0·9)	6·4(0·8)	−5·9	0·19
LDL cholesterol (mmol/l)				
M and M + PIR	4·8(0·9)	3·0(0·7)	−35·6	0·03
M and M	4·8(0·7)	4·3(0·9)	−10·3	0·19
HDL cholesterol (mmol/l)				
M and M + PIR	1·0(1·6)	1·5(0·4)	+49·3	0·06
M and M	1·1(0·2)	1·2(0·3)	+12·5	0·63
Triglyceride (mmol/l)				
M and M + PIR	3·1(2·0)	2·0(0·3)	−25·9	0·06
M and M	2·6(1·3)	2·1(0·8)	−12·0	0·63
Body mass index (kg/m^2)				
M and M + PIR	51·0(13·3)	34·5(4·3)	−32·4	0·03
M and M	50·4(6·8)	38·7(7·4)	−23·6	0·06

Values are mean(s.d.). M and M, Magenstrasse and Mill; PIR, partial ileal resection; LDL, low-density lipoprotein; HDL, high-density lipoprotein. *Wilcoxon rank sum test

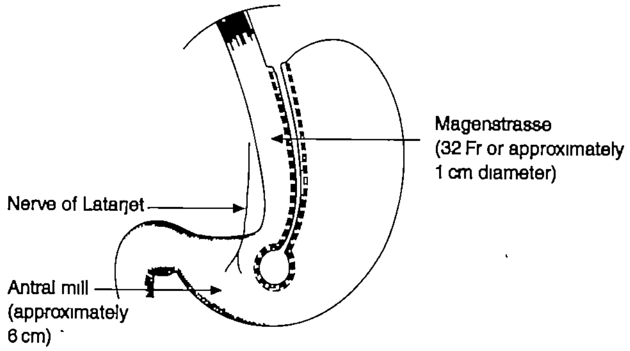

Fig. 1 The Magenstrasse and Mill operation

tube or Magenstrasse conveys food to the antrum (Mill) and pylorus, which remain intact to permit normal grinding and emptying. No foreign material band was used.

Approximately 150 cm of distal ileum (25 per cent of the small bowel length) was resected, with preservation of the terminal 10 cm of ileum and the ileocaecal sphincter. Continuity was restored by ileoileal anastomosis.

Results

There were no deaths. One patient developed a temporary fistula from the Magenstrasse after M and M plus PIR and another developed an incisional hernia after M and M alone. One year after operation, mean bowel frequency was 1·6 (range 1–2) per day in the M and M alone group compared with 2·8 (range 1–4) in the PIR group, none of whom experienced severe diarrhoea.

Addition of PIR to the M and M procedure led to mean decrease of 24 per cent in total cholesterol, 36 per cent in low-density lipoprotein, 26 per cent in triglycerides, and a 49 per cent increase in high-density lipoprotein levels (*Table 1*). Changes in lipids after M and M alone were not significant.

Discussion

This was a pilot study, involving a small number of patients and short follow-up. The results were encouraging; limited ileal resection led to profound changes in plasma lipids, similar in magnitude to those previously reported after the use of statins[3] or partial ileal bypass[1]. Unlike ileal bypass, PIR preserves the ileocaecal junction and has not produced the major changes in bowel function reported after ileal bypass[4]. Further cautious use of PIR seems justified, particularly in diabetic women who undergo bariatric surgery because they are at high risk of sustaining a coronary event after the menopause[5].

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Clinical study of adjuvant photodynamic therapy to reduce restenosis following femoral angioplasty

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Background: Photodynamic therapy (PDT) reduces neointimal hyperplasia and negative remodelling following balloon injury in small and large animal models. This clinical study investigated the role of adjuvant PDT following femoral percutaneous transluminal angioplasty (PTA).

Methods: Eight PTAs in seven patients (two women) with a median age of 70 (range 59–86) years were performed with adjuvant PDT. All patients had previously undergone conventional angioplasty at the same site which resulted in symptomatic restenosis or occlusion between 2 and 6 months. Each was sensitized with oral 5-aminolaevulinic acid 60 mg/kg, 5–7 h before the procedure. Following a second femoral angioplasty, up to 50 J/cm^2 red light (635 nm) was delivered to the angioplasty site via a laser fibre within the angioplasty balloon. Patients were kept in subdued light overnight and discharged the following day. Outcome was assessed by duplex imaging at 24 h, 1, 3 and 6 months and by intravenous digital subtraction angiography at 6 months. A peak systolic velocity ratio (PSVR) of more than 2·0 at the angioplasty site was taken to represent restenosis.

Results All patients tolerated the procedure well without adverse complications or death. All were rendered asymptomatic which was sustained throughout the study interval. All vessels remained patent and no lesion attained the duplex definition of restenosis. Median (interquartile range) PSVR across stenotic segments was 4·7 (3·7–5·7) before angioplasty, 1·1 (0·9–1·3) at 24 h and 1·4 (1·0–1·8) at 6 months after intervention ($P = 0·04$ compared with preoperative value).

Conclusion: This pilot study suggests that endovascular PDT is safe and may reduce restenosis following angioplasty. The data justify a randomized controlled trial.

Paper accepted 20 June 1999

British Journal of Surgery 1999, **86**, 1258–1263

Introduction

Restenosis remains the major limitation of percutaneous transluminal angioplasty (PTA) and other minimally invasive endovascular techniques. The incidence varies depending on the angioplasty site, the method of intervention and the type of surveillance after intervention. Restenosis follows 15–40 per cent of all angioplasties[1–6], the majority occurring within 6 months[6].

Research using animal models of restenosis and data from clinical trials suggests that restenosis has a multifactorial aetiology including a combination of neointimal hyperplasia (NIH)[7], matrix deposition and negative geometric remodelling[8,9]. Many therapies have been directed at reducing restenosis, some of which have been successful in experimental models, but few have been effective in clinical trials[10]. An exception, recently described in both animal[11] and clinical[12] studies, is intracoronary ionizing irradiation (brachytherapy) which decreases neointima formation and maintains larger lumen dimensions after PTA[13].

A new possibility for prevention of restenosis may be photodynamic therapy (PDT). This involves the interaction of non-ionizing, non-thermal light (usually low-power red light from a laser source) with a preadministered photosensitizing agent to produce reactive intermediates (mainly singlet oxygen) which are cytotoxic[14]. PDT has been studied extensively for the treatment of malignant and premalignant conditions[15], but its potential is now being explored for a range of non-neoplastic conditions. Over the past 5 years, evidence has accumulated that PDT can deplete the arterial media of vascular smooth muscle cells and reduce neointima formation following arterial injury in small animals[16]. 5-Aminolaevulinic acid (ALA) is a relatively new sensitizing agent that is converted into an active photosensitizer, protoporphyrin IX (PpIX) as part of the biosynthesis of haem. In a porcine model, PDT with the photosensitizer ALA reduced the vascular smooth muscle cell population of the arterial media[17] and, following an overdistension balloon injury, reduced NIH and negative remodelling[18,19].

The objective of this study was to investigate the safety and efficacy of adjuvant ALA-PDT following femoral angioplasty. The superficial femoral artery (SFA) was selected because of the relatively poor medium-term outcome of PTA in this segment[4,20–22] and the ease with which bypass surgery could be carried out in the event of unexpected complications. Patients were offered entry into this trial if they had previously undergone femoral PTA that had resulted in symptomatic restenosis; all suitable patients were offered bypass surgery as an alternative.

Patients and methods

Patients were recruited prospectively. They were excluded if they had pre-existing liver disease (ALA can cause increased levels of liver enzymes) or a complete femoral artery occlusion greater than 15 cm in length. Long occlusions were excluded because the anticipated technical problems might have made it difficult to judge the influence of PDT on restenosis. All patients were symptomatic and all lesions were confined to the SFA.

Symptoms and findings on examination were documented and baseline blood tests were performed. Ankle:brachial pressure index (ABPI) at rest and following a standard exercise protocol (4 min at 2 km/h with a 10° upward slope) were measured. An arterial duplex scan was performed; the lesion that had previously been angioplastied was visualized and restenosis confirmed. The distance from the centre of the stenosis to the medial femoral condyle was then measured and recorded. The peak systolic velocity ratio (PSVR) was calculated from the ratio of the peak systolic velocity at the stenosis to that at a normal prestenotic site. A PSVR greater than 2·0 across the lesion was taken to define a significant restenosis[23].

Patients were admitted for repeat PTA with adjuvant PDT. ALA was provided by DUSA Pharmaceuticals (Valhalla, New York, USA) in powder form and given in a total dose of 60 mg/kg in three divided measures dissolved in 50 ml orange juice over 2 h. After this, patients were kept in subdued lighting. Between 5 and 7 h after the first dose, patients underwent angiography via an ipsilateral femoral puncture and the stenosis was identified by comparison with previous films. Oxygen saturation was monitored using pulse oximetry and the probe rotated from finger to finger to avoid skin damage in a photosensitized patient[24]. Heparin 5000 units was given intra-arterially. Standard PTA using an appropriately sized (4–6 mm) transparent PTA balloon (Cordis, Roden, The Netherlands) was performed and angiography was repeated to confirm a satisfactory result. The guidewire was then exchanged for a 200 μm laser fibre (Rare Earth Medical, West Yarmouth, Massachusetts, USA) with a 4-cm diffuser to match the balloon length. Some 50 J/cm^2 light at a wavelength of 635 nm (power less than 120 mW/cm^2) was given from a copper vapour pumped dye laser (Oxford Lasers, Oxford, UK). The laser beam was interrupted to provide a fractionation break of 60 s after 20 per cent of the dose as this has been shown to improve the effect of PDT in both animal and clinical studies[25,26].

Completion angiography was performed and the run-off vessels were identified. Patients were kept in subdued lighting overnight and underwent duplex imaging the following day. They were then reassessed at 1, 3 and 6 months, when they had intravenous digital subtraction angiography (DSA). Angiograms were reviewed blindly by a consultant radiologist and the degree of narrowing at the treatment site was compared with the initial postangioplasty arteriogram. All angiograms were performed in the same radiological suite using the same magnification. Individual angiograms were checked by measuring the distance between the medial and lateral femoral cortex. Restenosis was assessed by measuring the percentage lumen loss, estimated by comparing the lumen width in millimetres with calipers at 6 months with that measured immediately after angioplasty.

Data were expressed as median (interquartile range) and compared using Wilcoxon signed rank test with significance taken at the 5 per cent level. Liver function was assessed on day 1 and at 1 month. All patients received aspirin 75 mg per day for life.

Results

Seven patients (two women and five men) with a median age of 70 (range 59–86) years underwent eight angioplasties with adjuvant PDT. Risk factors for peripheral vascular disease included hypertension (three), diabetes mellitus (two) and smoking (three). Three patients had an occluded SFA (less than 5 cm in length) and the other five lesions in four patients were greater than 75 per cent stenoses less than 10 cm in length. Following previous successful PTA, three patients re-presented with angiographically proven restenosis at 2 months; one at 3 months; two at 5 months and one at 6 months after intervention. In this study, all lesions were again successfully dilated under radiological imaging with satisfactory immediate results, and no complications.

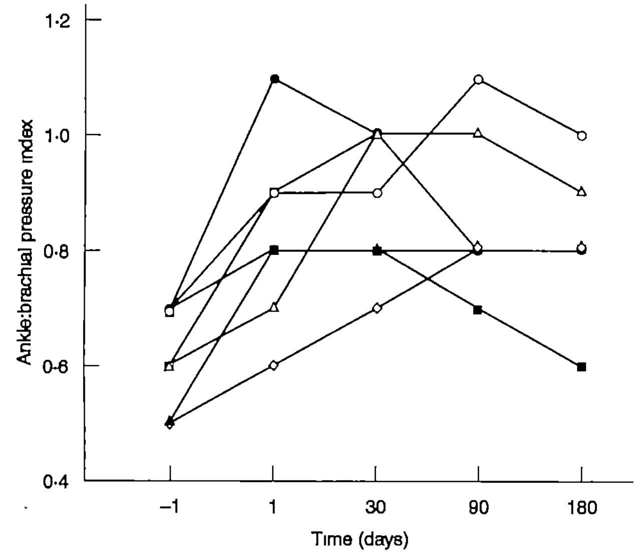

Fig. 1 Ankle : brachial pressure index data for all legs before angioplasty and at 24 h, 1, 3 and 6 months after the procedure

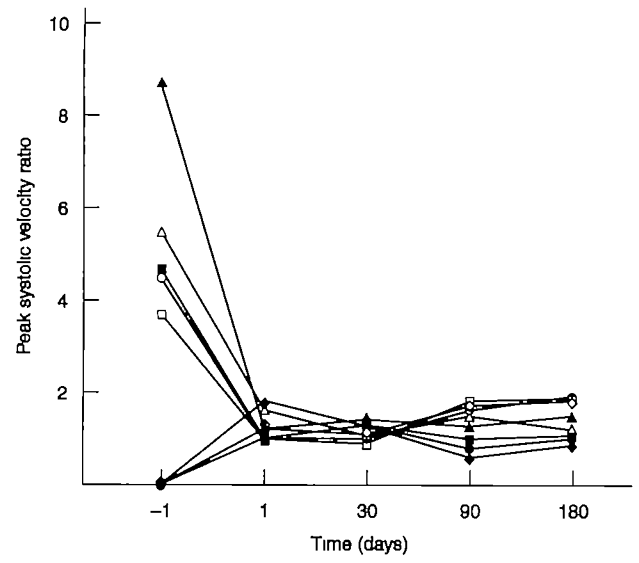

Fig. 2 Peak systolic velocity ratio for all legs before angioplasty and at 24 h, 1, 3 and 6 months after the procedure

Surveillance

At follow-up, all patients were asymptomatic at 1 month and remained asymptomatic (with walking distance not limited by claudication) throughout the study. In two patients, a fall in ABPI from the value obtained immediately after the procedure was noted, but in others the ABPI remained stable or continued to improve during the 6-month study (*Fig. 1*). Using the PSVR measurement derived from duplex analysis, none of the angioplasty segments reached a PSVR greater than 2, the definition of restenosis[23] (*Fig. 2*). The initial PSVR before angioplasty showed that all arterial lesions were composed of significant stenoses (PSVR greater than 2) or occlusions (PSVR 0). Median (interquartile range) PSVR across stenotic segments was 4·7 (3·7–5·7 (excluding occlusions) before angioplasty; 1·1 (0·9–1·3) at 24 h and 1·4 (1·0–1·8) at 6 months after intervention ($P = 0·04$ compared with preoperative value). Including the occluded segments (with a PSVR of zero) in the statistical analysis lowered the preoperative median PSVR from 4·7 (3·7–5·7) to 4·1 (1·6–6·7), and reduced the significance of the difference at 6 months ($P = 0·09$).

At 6 months, intravenous DSA confirmed patency in all cases (*Fig. 3*). Percentage stenosis as measured at angiography was calculated for all lesions. In three cases there was no evidence of radiological restenosis; three had a 25 per cent restenosis and two 40 per cent.

One patient experienced a transient rise in liver enzymes, and another mild nausea and temporary facial erythema. These side-effects have been described previously[27] with use of ALA photosensitization. Side-effects were mild and resolved spontaneously in both patients.

Discussion

This is the first clinical trial of adjuvant arterial PDT to prevent restenosis following angioplasty. No major complications were noted at the time of the procedure and follow-up to 6 months has revealed no evidence of clinical restenosis.

A prerequisite for a therapy to prevent restenosis is that it is compatible with angioplasty. The minimally invasive, percutaneous nature of angioplasty has revolutionized the treatment of cardiovascular disease and any adjuvant treatment must be as safe and acceptable to physicians and patients alike. A long period of skin photosensitivity, for example, would be unacceptable.

ALA was thought to be the ideal photosensitizer for targeting the vascular system as data from the pig model revealed excellent PpIX fluorescence in the arterial wall[27] and ALA-PDT, using intra-arterial illumination, resulted in minimal extravascular effects[17]. An oral dose of 60 mg/kg was selected as this is the highest dose with an established safety profile[28,29]. This was given in three divided doses to give a longer plateau phase and to avoid a postbolus peak[30]. There is scant information on the optimum drug–light interval for ALA-PDT in humans, but previous studies would suggest a plasma PpIX half-life of 8 h[29] with maximum tissue concentrations reached in a variety of tissues 7–10 h after oral administration[28]. Other studies on patients undergoing procedures for gastrointestinal and colorectal malignancies have shown that peak fluorescence

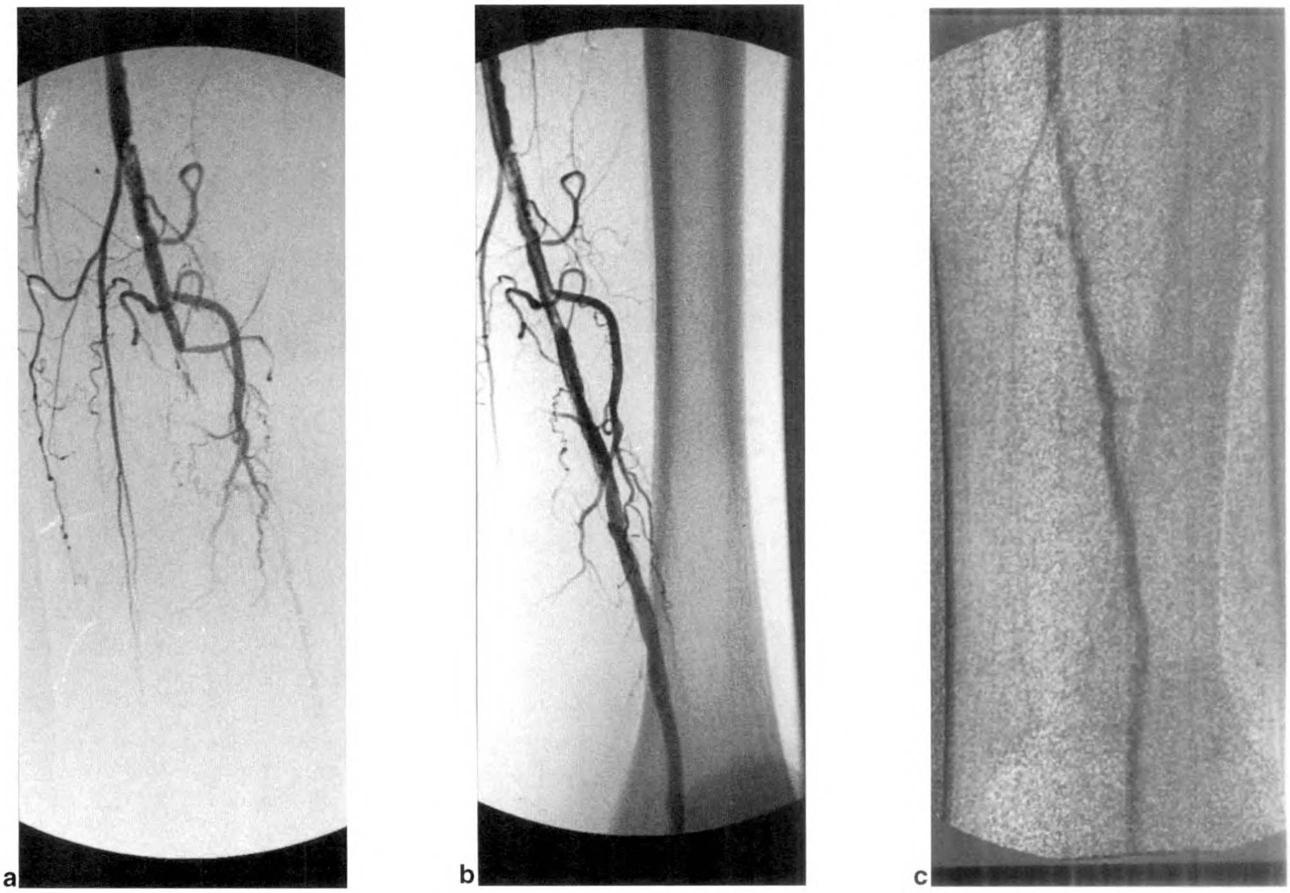

Fig. 3 Left femoral angiogram of a superficial femoral artery occlusion:
a before angioplasty,
b the immediate result following percutaneous transluminal angioplasty and adjuvant photodynamic therapy and
c intravenous digital subtraction angiography at 6 months

activity is reached 6 h after oral ALA is given as a bolus[31] or in divided doses[30]. For the present study a drug–light interval of 5–7 h was chosen.

The skin photosensitivity interval of 24–48 h and drug–light interval of the order of 5 h make ALA-PDT a feasible adjuvant to angioplasty, necessitating only one night in hospital. Light delivery at the time of angioplasty was easily accomplished in the vascular suite and use of the same balloon for angioplasty and as a vehicle for light transmission meant minimal delay and catheter manipulation during the procedure.

In this small cohort of patients judged to be at high risk of restenosis, little evidence of restenosis was seen within the study interval. Review of the intravenous DSA films at 6 months revealed that in two patients a degree of narrowing occurred, but this did not encroach on greater than 50 per cent of the lumen. Both these patients remained asymptomatic and the haemodynamic significance of the radiological findings must be questioned. A limitation of angiography is that it gives a uniplanar anatomical view which may be of little relevance to function and is inaccurate for eccentric lesions. Duplex imaging gives anatomical information in more than one plane and can therefore identify eccentric plaques in addition to documenting the disturbance in flow caused by a stenosis. No lesions attained the predetermined duplex definition of restenosis at the end of the surveillance interval.

It is impossible to predict the expected restenosis rate in such a small group of patients, but the evidence from other series would suggest that it should be higher than was observed. Three patients in this series had an occluded artery initially and the reported success rates for first-time recanalization of an occluded femoral segment range from 22 to 44 per cent after 1 year[22,32]. Even with stenotic disease, patency rates at 1 year are less than 50 per cent[20,21] and most would agree that results with restenotic lesions are probably worse[33,34].

The results of this pilot study suggest that PDT is effective in reducing restenosis following angioplasty, although the number of patients studied was small and it would be premature to claim that ALA-PDT abolishes restenosis. However, the results are sufficiently promising to justify a randomized controlled trial of angioplasty with adjuvant PDT.

Acknowledgements

This study was funded by the Sir Jules Thorn Charitable Trust.

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Comparison of the expression of fibrosis-associated genes in glomeruli after renal transplantation between conventional cadaveric and non-heart-beating donors

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Background: The main difference between cadaveric heart-beating donors and non-heart-beating donors (NHBDs) is the degree of warm ischaemia to which the kidney is subjected. This study was designed to see if this affected the expression of fibrosis-associated genes in the early period after transplantation.

Methods: A series of 29 cadaveric and 19 NHBD renal transplants was studied. Patients underwent protocol needle-core renal transplant biopsies at 1 week, 3 months and 6 months after transplantation. At least two individual glomeruli were isolated from each biopsy. Messenger RNA was extracted and genes of interest were amplified by reverse transcriptase–polymerase chain reaction, then quantified in an enzyme-linked immunosorbent assay system.

Results: Delayed graft function was common in NHBD (17 of 19) compared with cadaveric transplants (six of 29) ($P < 0.0001$). Acute rejection rates were similar. The level of tissue inhibitor of metalloproteinase 1, an inhibitor of extracellular matrix degradation, was higher in kidneys from NHBDs at 1 week ($P = 0.02$). There were no other statistically significant differences in the expression of fibrosis-associated genes between the two groups.

Conclusion: Although the increased ischaemic injury in kidneys retrieved from NHBDs leads to a higher rate of delayed graft function, this does not translate into increased expression of fibrosis-associated genes after the first week.

Paper accepted 6 June 1999

British Journal of Surgery 1999, **86**, 1264–1268

Introduction

There continues to be a critical shortage of kidneys for transplantation in the UK[1]. The use of non-heart-beating donor (NHBD) kidneys has been proposed as one method of improving the organ shortage problem. Many transplant surgeons are, however, reluctant to consider using NHBD kidneys on the grounds that they have been subjected to a significant amount of warm ischaemic damage. This has led to concerns that NHBD kidneys may be more susceptible to the development of chronic allograft nephropathy (CAN) and that this would be reflected in poorer long-term graft survival. The pathogenesis of CAN is complex and incompletely understood, but early endothelial ischaemic injury is thought to be an important factor leading to a cascade of cytokine and growth factor production that eventually causes graft fibrosis[2].

The aim of this study was to compare the expression of various fibrosis-associated genes in renal transplants from conventional brainstem-dead heart-beating cadaveric donors and NHBDs.

Patients and methods

Patients

A series of 48 patients undergoing renal transplantation between April 1996 and April 1998 was studied. Immunosuppressive regimens during this period were based on either Neoral (Novartis Pharmaceuticals, Camberley, UK) cyclosporin or tacrolimus (Prograf; Fujisawa, London, UK). For recipients of heart-beating donor kidneys the dosing protocol was as follows: either cyclosporin at 15 mg per kg per day reducing to 5 mg per kg per day at 6 weeks or tacrolimus 0·2 mg per kg per day. In view of their higher rate of delayed graft function, NHBD kidney transplant recipients received lower doses of calcineurin inhibitors as follows: either cyclosporin 7 mg per kg per day reduced to 5 mg per kg per day at week 2 after transplantation or tacrolimus 0·1 mg per kg per day. All patients received prednisolone 20 mg/day for 3 months with a tapered reduction to 10 mg on alternate days by 6 months after transplantation. NHBD kidney transplant recipients also received azathioprine 1–2 mg per kg per day as part of their triple regimen.

Biopsies

Protocol day-case needle-core biopsies were performed at 1 week, 3 months and 6 months after transplantation. They were done under real-time ultrasonographic guidance using a 16-G Tru-Cut needle (Travenol Laboratories, Deerfield, Illinois, USA) mounted in a spring-loaded biopsy gun. All biopsies were examined under a stereoscopic microscope to check for the presence of renal cortex. Two individual glomeruli were plucked from the cortex using ultrafine forceps and immediately placed into lysis binding buffer to prevent messenger RNA (mRNA) breakdown.

Molecular analysis

This has been described in detail previously[3,4]. In brief, mRNA was extracted from glomeruli using oligo-dT-linked Dynabeads (Dynal, Bromborough, UK). Competitive reverse transcriptase–polymerase chain reaction (RT–PCR) was then performed as already described[4]. The genes chosen for study were the matrix proteins collagen III, collagen IV α2 chain and tenascin, the enzyme matrix metalloproteinase (MMP) 2, tissue inhibitors of metalloproteinases (TIMPs) 1 and 2, and transforming growth factor (TGF) β. All primers and probes were designed on sequences obtained from the EMBL database using the program GCG prime (Genetics Computer Group, Madison, Wisconsin, USA) and synthesized by Life Technologies (Paisley, UK) or Genosys Biotechnologies Europe (Pampisford, UK). Quantification of RT–PCR products was performed in an enzyme-linked immunoassay system as described[4]. Competitive RT–PCR allowed correction for differences in efficiency between PCRs, and differences in the cellularity of glomeruli were controlled for by expressing values of complementary DNA product as a ratio to that of a constitutively expressed housekeeping gene, glyceraldehyde phosphate dehydrogenase. The expression of individual genes was calculated in arbitrary units derived from this ratio.

Statistical analysis

Gene expression was assessed in two glomeruli from each biopsy and the mean of these two corrected values was taken for comparative purposes. The Kruskal–Wallis test was used to analyse differences in individual gene expression between biopsies from the two groups at the three time points used.

Results

Clinical details

In total 48 patients (29 cadaveric donor, 19 NHBD), had biopsies from at least one of the time points under study and a total of 90 biopsies was analysed. *Table 1* shows the characteristics of these patients. Both recipient and donor ages were greater in the NHBD group, which also contained a significantly greater proportion of men. A

Table 1 Patient characteristics

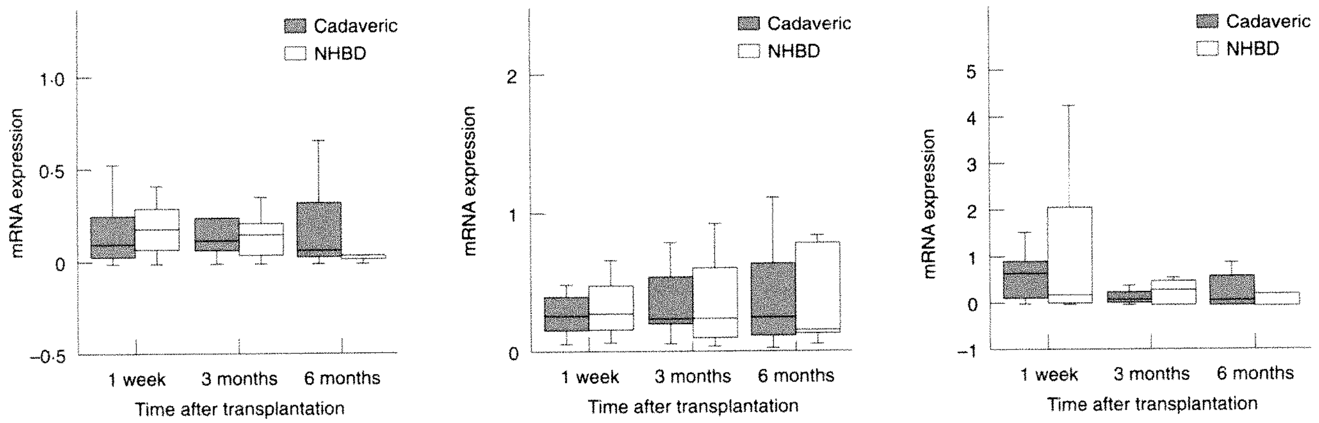
	Heart-beating donor (*n*=29)	Non-heart-beating donor (*n*=19)	*P*
Recipient age (years)*	42(13)	49(11)	0·03‡
Recipient sex ratio (M : F)	14 : 15	15 : 4	0·04§
Donor age (years)*	38(15)	49(11)	0·003‡
HLA-DR mismatch	16	12	0·40§
Ischaemic times*			
First warm (min)†	0	22(8)	< 0·0001‡
Cold (h)	16(7)	15(5)	0·69‡
Drug therapy			
Cyclosporin A	13	9	0·54§
Tacrolimus	16	10	

*Values are mean(s.d.). †First warm time applies only to non-heart-beating donors and is the period of absolute circulatory standstill during which cardiopulmonary resuscitation is stopped and death confirmed. HLA, human leucocyte antigen. ‡Student's *t*-test; §Fisher's exact test

Table 2 Early outcome

	Heart-beating donor (*n*=29)	Non-heart-beating donor (*n*=19)	*P*
Primary non-function†	1	2	0·34¶
Delayed graft function‡	6	17	< 0·0001¶
Acute rejection§	10	5	0·39¶
Six-month creatinine (μmol/l)*	131 (103–192)	180 (130–305)	0·06**

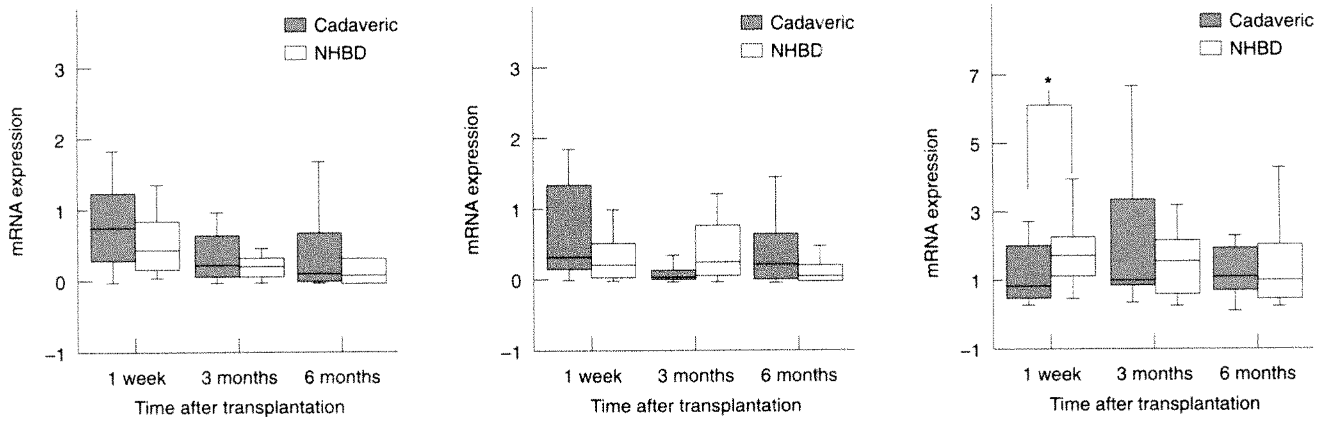
*Values are median (interquartile range). †Failure to become independent of dialysis; ‡need for dialysis in the first week after transplantation, excluding correction of metabolic abnormalities; §acute rejection episode by 6 months confirmed histologically. ¶Fisher's exact test; ** Mann–Whitney *U* test



a TGF-β

b Collagen III

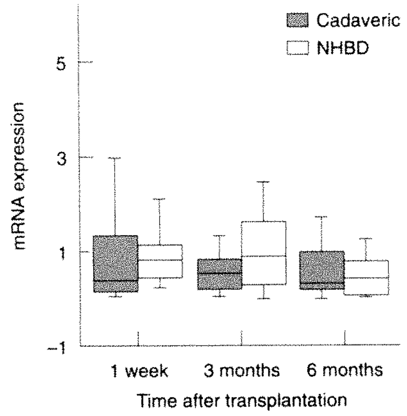
c Collagen IV α2 chain



d Tenascin

e MMP-2

f TIMP-1



g TIMP-2

Fig. 1 Comparative messenger RNA (mRNA) expression between kidneys from cadaveric and non-heart-beating donors. Boxes represent interquartile ranges and horizontal lines within boxes show median values. Vertical lines extend to maximum and minimum observed values with 1·5 box lengths. NHBD, non-heart-beating donor; TGF, transforming growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of MMP. $^*P = 0{\cdot}02$ (Kruskal–Wallis test)

difference in warm ischaemic time between the two donor groups was recorded (mean warm time 0 *versus* 22 min); cold ischaemic times were similar. Both groups had a similar proportion of patients on cyclosporin or tacrolimus drug therapy.

The early outcome of transplants from the two groups is compared in *Table 2*. There was no significant difference in the rates of primary non-function but delayed graft function was much commoner in the NHBD group, affecting 17 of 19 patients compared with six of 29 who received kidneys from conventional cadaveric donors ($P < 0{\cdot}0001$). The acute rejection rates in the two groups were comparable. After 6 months, recipients of NHBD kidneys tended to have a higher mean serum creatinine level ($P = 0{\cdot}06$).

Intragraft gene expression

Comparative levels of mRNA expression between the two donor types are shown in *Fig. 1*. There were no statistically significant differences in the levels of intragraft (glomerular) gene expression for TGF-β, collagen III, collagen IV α2, tenascin or MMP-2. In the series of 1-week post-transplant biopsies, the expression of TIMP-1 was significantly higher in kidney transplants from NHBDs compared with those from heart-beating donors ($P = 0{\cdot}02$). The level of TIMP-2 transcripts was also higher at 1 week in grafts from NHBDs although the difference did not reach statistical significance. The levels of TIMP-1 and -2 at later time points were similar in the two groups.

Discussion

Although CAN may take several years to become clinically evident, it is likely that the underlying molecular changes are initiated in the first few weeks and months after transplantation[2]. The present study has demonstrated that in this interval there are few differences in the expression of fibrosis-associated genes in glomeruli taken from kidney transplants derived from conventional brain-dead heart-beating cadaveric donors and NHBDs. TIMP-1 expression was significantly higher in kidneys from NHBDs at 1 week after transplantation, and the levels of TIMP-2 also tended to be greater. These enzyme inhibitors are important in extracellular matrix remodelling, acting by inhibiting the collagen-digesting enzymes such as MMP-2[5]. TIMP-1 has also been shown to act as a growth factor for fibroblasts[6]. The increased expression of TIMP-1 in kidneys from NHBDs at this early time point may reflect changes in matrix turnover in response to damage caused by warm ischaemia. The raised levels did not persist and expression of both TIMPs and MMP-2 was similar in the two groups at 3 and 6 months.

TGF-β, a cytokine central to fibrosis in many diseases[7], was expressed at similar levels in both groups. The persistent overexpression of TGF-β is thought to occur in response to agents that cause graft damage and has been linked with CAN[8]. There was also no increased expression of the matrix proteins collagen III, collagen IV α2 chain or tenascin in kidneys from NHBDs compared with those from cadaveric donors. Both tenascin and collagen III have been shown previously to be present at increased levels in dysfunctional renal transplants[9,10], and increased deposition of extracellular matrix in 6-month protocol renal transplant biopsies has previously been shown to correlate with long-term renal function[11].

The essential difference between conventional heart-beating donors and NHBDs is the degree of warm ischaemic damage suffered before organ retrieval. Increased warm ischaemia in NHBDs is reflected in a poorer initial function, as seen by the increased rate of delayed graft function and the tendency to a raised serum creatinine level at 6 months after transplantation. Both of these factors are predictors of poorer long-term prognosis. The data presented here demonstrate that NHBD kidneys do not overexpress a number of fibrosis-related genes after transplantation and, although different immunosuppression regimens in the two groups may have been a factor, this suggests that warm ischaemic injury does not predispose to CAN. The assumption has been made that the expression of fibrosis-associated genes is a surrogate marker of future CAN; confirmation will require continuation of this study to show that these effects are carried through to the protein level, and eventually to histological CAN and graft failure. Previous reports have shown that, despite poor early function, the medium- to long-term results of NHBD kidney transplants are similar to those from conventional heart-beating cadaveric donors[12–14]. The findings in this paper may offer a molecular explanation for these graft survival data.

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Oral nifedipine reduces resting anal pressure and heals chronic anal fissure

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Background: Topical preparations have been used in the treatment of anal fissure. However, they are not universally successful and there is confusion over the site and dose of application. This study assessed the effectiveness of oral nifedipine in reducing resting anal pressure and on fissure healing.
Methods: Anal manometry was performed on eight healthy volunteers and 15 patients with chronic anal fissure before and after oral administration of nifedipine 20 mg. Nifedipine was taken twice daily. Fissure healing was assessed over an 8-week period and pain scores were monitored.
Results: Oral nifedipine produced an initial reduction in maximum resting anal pressure (MRP) of 35 per cent ($P < 0.001$) and of 28 per cent after 5 days ($P < 0.001$) in healthy volunteers. A reduction in MRP of 36 per cent ($P < 0.001$) was observed in patients with fissure. Pain scores were significantly reduced during the treatment period. Healing was complete in nine patients after 8 weeks and a further three were asymptomatic. Ten patients experience flushing and four had mild headaches. There were no episodes of postural hypotension or incontinence.
Conclusion: Oral nifedipine reduces resting anal pressure. It is well tolerated and offers an alternative treatment for chronic anal fissure.

Paper accepted 22 July 1999

British Journal of Surgery 1999, 86, 1269–1273

Introduction

Anal fissures are associated with increased resting anal pressure due to internal anal sphincter (IAS) hypertonia. Surgery has been the traditional treatment but this results in irreparable damage to the IAS. There has been increasing concern over the long-term outcome of these procedures with up to one-third of patients experiencing some form of incontinence[1]. Recently, attention has therefore focused on finding a suitable alternative means of reducing sphincter pressure while leaving the sphincter intact.

Glyceryl trinitrate (GTN; a nitric oxide donor) paste has been used successfully and results in fissure healing in around two-thirds of patients[2]. However, some patients experience tachyphylaxis, whereby increasing concentrations of paste are required to maintain an effect[3], and there is a high incidence of side-effects, particularly headache, forcing some participants to stop using the medication[4]. Furthermore, there may be confusion as to whether paste should be applied around the anal margin or within the anal canal, and the volume of paste that should be applied may also be unclear.

Calcium ions are important for smooth muscle contraction and L-type calcium channel (the principal calcium channel in smooth muscle) antagonists such as nifedipine have been used with variable results in the management of achalasia[5,6]. Recent *in vitro* studies have shown that nifedipine produces an abolition of resting tone and attenuation of agonist-induced contractions in IAS smooth muscle[7].

An oral preparation could overcome some of the potential confusion with site of application and dose, and may also increase compliance. However, the use of oral nifedipine has been attempted in the management of detrusor instability with little effect and there is some suggestion in animal models that this may be due to downregulation of calcium channels, an effect that occurs within a few days of starting treatment[8]. The aim of this study initially, therefore, was to establish whether oral nifedipine has an effect on resting anal pressure over a 5-day period and subsequently to assess its effectiveness in healing chronic anal fissure.

Patients and methods

Healthy volunteers and patients with chronic anal fissure were studied. Individuals with cardiovascular disease or those who were pregnant or breastfeeding were excluded.

Local ethics committee approval was obtained for the study, and all volunteers and patients gave informed consent. An initial investigation of healthy volunteers was used to establish whether oral nifedipine had an effect on resting anal pressure over a 5-day period. The second part of the study assessed the effectiveness of nifedipine in healing of chronic anal fissure.

Manometry

Anal manometry was performed in the left lateral position. A station pull-through technique was employed using a small air-filled microballoon. Pressures were measured before and 40 min after administration of nifedipine 20 mg (Adalat; Bayer Pharmaceuticals, Newbury, UK). Participants were then given nifedipine retard (Adalat Retard; Bayer Pharmaceuticals) 20 mg twice daily. Doses were chosen after discussion with cardiologists and with the manufacturer. Nifedipine (a rapidly acting preparation) was given initially to permit repeated measurements in a short time period. Nifedipine retard was selected to give a smoother release of the drug with potentially fewer side-effects. Blood pressure was monitored.

Healthy volunteers

Volunteers were treated initially as described above. They were seen again on the fifth day and manometry was repeated 2·5 h after the final dose of nifedipine retard.

Patients

Patients with chronic anal fissure, defined as a fissure lasting for more than 2 months, with failure of simple analgesics and stool softeners, were recruited to the study. Manometry was performed at the first visit and pain was assessed using a linear analogue scale ranging from 'no pain' to 'worst pain imaginable'. The patients were given nifedipine retard and were seen in the clinic every fortnight to monitor fissure healing. Blood pressure and pain scores were recorded (average pain over the preceding fortnight) at each visit. Patients in whom the fissure healed were discharged. If no healing was noted by 8 weeks, they were offered either a course of GTN paste or lateral sphincterotomy. Patients were followed for a minimum of 3 months.

Statistical analysis

Manometric data were expressed as mean(s.d.). Comparisons between the groups were made using an unpaired *t* test and those between paired data using a paired *t* test with correction for multiple comparisons where appropriate. Pain scores were expressed as median (range) and comparison between scores was made using a Wilcoxon test, with correction for multiple comparisons.

Results

Healthy volunteers

Eight people (five women), of median age 31 (range 20–35) years, were recruited. Mean maximum resting anal pressure (MRP) fell significantly from 85(11) to 54(8) cmH_2O ($P < 0.001$) after the initial dose of nifedipine. After 5 days of treatment, there was a continued reduction with a mean resting anal pressure of 62(9) cmH_2O ($P < 0.001$) (*Fig. 1*). These falls represent reductions from pretreatment pressures of 35(5) and 28(6) per cent respectively. Pretreatment mean maximum squeeze pressure was 122(34) cmH_2O; there was no significant difference after the initial dose of nifedipine (121(34) cmH_2O; $P = 0.84$) or following 5 days of treatment (128(38) cmH_2O; $P = 0.31$). Mean diastolic blood pressure fell initially from 77(8) to 71(7) mmHg ($P = 0.035$) but was not significantly different from pretreatment levels after 5 days (76(9) mmHg; $P = 0.61$).

Nifedipine was associated with flushing, principally of the lower limbs and face, in six people and mild headache in two. These side-effects were most pronounced after the initial dose of nifedipine and improved with time when taking nifedipine retard. Nobody complained of light-headedness or feeling faint and there were no episodes of incontinence.

Patients

Fifteen patients (eight women), of median age 43 (range 20–60) years, with chronic anal fissure were entered into the study. Median duration of symptoms was 15 (range 5–240) months. Fissures were situated posteriorly in 12 patients, anteriorly in one, and two patients had both anterior and posterior lesions. Resting pressures were higher in patients than volunteers (102(21) *versus* 85(11) cmH_2O; $P = 0.049$). The initial dose of nifedipine caused a 36(11) per cent fall in mean MRP from 102(21) to 65(20) cmH_2O ($P < 0.001$) (*Fig. 2*). Again no change was seen in the maximum squeeze pressure following nifedipine (93(44) *versus* 95(46) cmH_2O; $P = 0.34$).

Diastolic blood pressure fell after the first dose (82(8) to 75(7) mmHg; $P < 0.001$) and there was still a slight reduction compared with pretreatment levels after 2 weeks. However, by 4 weeks diastolic blood pressure was not significantly different from pretreatment levels. Pain scores were significantly reduced after 2 weeks and continued to show a reduction throughout the treatment period (*Table 1*).

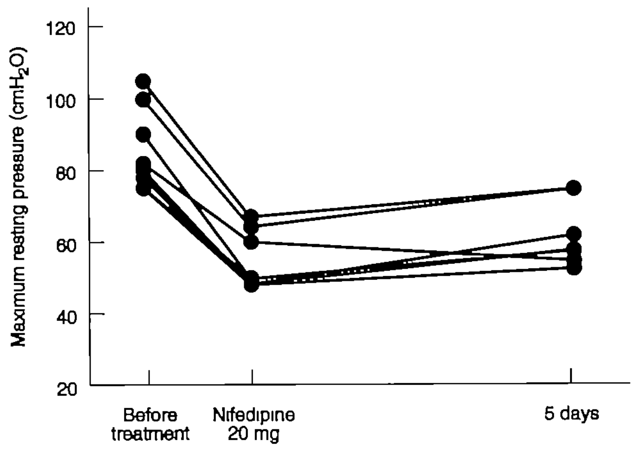

Fig. 1 Maximum resting anal pressures in eight healthy volunteers before and after nifedipine 20 mg, and following 5 days' treatment with nifedipine retard

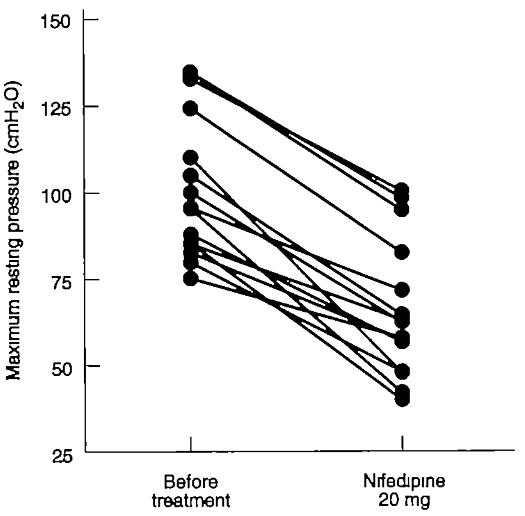

Fig. 2 Maximum resting anal pressures in 15 patients with chronic anal fissure before and after nifedipine 20 mg

One 60-year-old woman developed a prolonged headache after the initial dose of nifedipine and withdrew from the study within 24 h of entering. On close questioning she admitted that the onset of the headache had preceded ingestion of the capsules and she also had a history of migraine attacks. Four other patients developed mild headaches that responded to simple analgesics. Ten patients noticed flushing and one had mild ankle oedema. All side-effects occurred in the first 4 weeks of the study. No patient developed postural hypotension and there were no episodes of incontinence.

Three fissures were healed by 6 weeks and a total of nine after 8 weeks, including four that had failed to heal with GTN paste. A further three patients were asymptomatic and declined further treatment. One patient, whose treatment with nifedipine failed, healed with GTN paste and one underwent lateral sphincterotomy. There was one recurrence in the first month and this responded to topical treatment with GTN.

Discussion

This study has demonstrated that an oral preparation of nifedipine leads to a reduction in MRP and that this effect is maintained over a few days in healthy volunteers. This latter point is important because use of this agent to treat other pathologies has been difficult because of rapid development of tolerance to nifedipine[8]. However, the IAS has pharmacological properties similar to those of vascular smooth muscle[9,10], which clearly has a prolonged response to nifedipine, and it is therefore not surprising that a sustained response was observed in the IAS. Although the percentage reduction in MRP after 5 days was less than the initial response, data from the manufacturer reveal that peak plasma nifedipine concentrations are lower after nifedipine retard than following administration of nifedipine and this lower plasma level may explain the slightly reduced response.

Although the MRP was higher in the patient group, the percentage reduction in MRP following the initial dose of nifedipine was similar between the volunteer and patient groups. Repeated manometry was avoided in patients with painful fissures and 5-day values were therefore not available for this group. However, it is not unreasonable to expect similar responses between the two groups to prolonged application. Patients previously treated with GTN had had no therapy for at least 1 month before taking nifedipine and it is therefore unlikely that nifedipine and GTN had an additive effect in this subgroup. Nifedipine has little effect on skeletal muscle and there was no difference in the squeeze pressures (a function of the external anal sphincter) before and after treatment.

Similar reductions in MRP have been noted with GTN paste[2]. Oral indoramin (an α-adrenergic antagonist) also caused a reduction in MRP of 36 per cent[11]. Jonard and Essamri[12] showed that oral diltiazem caused a 20 per cent reduction in resting anal pressure. A more recent report demonstrated similar reductions in MRP with oral and topical diltiazem but found that the oral preparation was associated with postural hypotension[13]. However, unlike diltiazem, nifedipine has little action on cardiac muscle and one might reasonably expect there to be fewer side-effects.

A single dose of sublingual nifedipine has previously been shown to reduce MRP[14] but the present study represents the first report of an oral preparation being used successfully to treat chronic anal fissure. Healing was seen in nine of 15

Table 1 Median pain scores over the 8-week treatment period

	Pain score	P^*
Initial visit	57 (4–94)	—
2 weeks	31 (6–83)	0·016
4 weeks	30 (2–49)	0·017
6 weeks	4 (0–35)	0·004
8 weeks	5 (0–29)	0·013

Values are median (range). Pain score ranged from 0 (no pain) to 100 (worst pain imaginable). **Versus* pretreatment values (Wilcoxon test)

patients and a further three were symptom free after the treatment period. There was a significant reduction in pain scores within the first 2 weeks of treatment which continued throughout the period of study. Nifedipine has previously been used to treat anal pain associated with hypertension to good effect, albeit in an isolated report[15]. The continued reduction in pain over the treatment period and the alleviation of symptoms in three patients in whom the fissure failed to heal further supports a role for nifedipine in the treatment of anal fissure.

A potential criticism of using an oral agent is that higher doses may be needed to evoke an effect on the IAS than might be needed if a topical agent was used and that this could result in more side-effects. Nifedipine was developed as an antihypertensive agent and indeed there was an initial fall in diastolic blood pressure in both groups. However, there were no side-effects associated with the initial slight reduction in diastolic pressure. Nifedipine is known to have a greater effect at higher blood pressures and this study excluded patients with a history of hypertension. Follow-up measurements of diastolic blood pressure were not significantly different from pretreatment levels.

The principal side-effect associated with oral nifedipine was flushing of the face and limbs. However, this was usually short-lived, lasting less than an hour, and was more pronounced during the early stages of treatment. A smaller number developed mild headaches which responded to simple analgesics. Although one patient withdrew from the study because of a headache after the initial dose of nifedipine, close questioning revealed that this had preceded ingestion of the tablet and that she was prone to migraine attacks. In future it may be better to avoid nifedipine in patients with a history of headaches. None of the other patients found that the side-effects interfered with their daily activities.

Calcium channel antagonists offer an alternative means of reducing resting anal pressure to permit fissure healing. The main pharmacological agents used previously have been nitrates, which result in healing in two-thirds of patients[2]. Perianal injection of botulinum toxin to reduce MRP has also been used with a similar healing rate[16]. However, this requires injection of the toxin into the IAS and perianal thrombosis has been reported[17]. Seven of the 15 patients in this study had previously failed or been unable to tolerate treatment with GTN paste. Direct comparison of healing rates with other studies is therefore difficult as half of the present group had been shown to be resistant to one form of pharmacological treatment. However, the results are nevertheless encouraging with oral nifedipine healing fissures in nine patients, including four who had a history of failed treatment with GTN paste. Further studies are needed to determine whether the dosage used in this study is optimal for all patients. Oral nifedipine offers an alternative means of reducing resting anal pressure to allow healing of chronic anal fissure. There is no confusion over the site or dose of application, which represents a potential advantage over topical preparations. Further trials are now needed to compare oral nifedipine formally with other pharmacological preparations.

Acknowledgements

T.A.C. was in receipt of a research fellowship from the Royal College of Surgeons of England.

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Treatment and outcome of intracystic papillary carcinoma of the breast

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Paper accepted 20 June 1999

Introduction

Intracystic papillary carcinoma (IPC) of the breast is a rare form of *in situ* cancer, reported to represent 0·5 per cent of breast cancers in women[1–5]. If completely excised, pure IPC is associated with an excellent prognosis[1]. Reports on the accuracy of preoperative assessment by conventional radiological and cytological techniques vary in specificity[2]; excision biopsy remains the main method of achieving a definitive diagnosis. There is no consensus in the management strategy of IPC. Mastectomy, axillary dissection and radiotherapy are performed in many patients[3–5].

Patients and methods

This study was a retrospective analysis of all patients diagnosed with IPC of the breast at the Royal Marsden Hospital between 1979 and 1997. Pathology slides and hospital case notes were reviewed.

Results

A total of 23 patients with IPC presented over 18 years. Pure IPC was diagnosed in 14 patients, five had associated ductal carcinoma *in situ*, one lobular carcinoma *in situ* and three had associated invasive cancer. The mean tumour size was 2·4 (range 1–7) cm. All patients were women with a mean age of 64 (median 65, range 38–88) years. The mean follow-up was 52·5 (median 42, range 4–158) months.

Of the 14 patients with pure IPC, 11 presented with a painless lump, one with asymmetric nodularity, one with bloody nipple discharge and one asymptomatic woman was detected at screening. The results of triple assessment are summarized in *Table 1*.

Treatment of the 14 patients with IPC alone varied significantly, indicating differing views on management and varying trends over the time of this study. Seven patients had local excision alone, of whom three received tamoxifen, one had radiotherapy with tamoxifen and three had no further treatment. Six patients had local excision and axillary dissection, two of whom received further tamoxifen and one had adjuvant radiotherapy. One patient underwent mastectomy and axillary dissection with no further treatment. None of the seven patients who had axillary dissection had lymph node involvement.

Table 1 Results of triple assessment in the detection of intracystic papillary carcinoma in 23 patients

	Method of detection			
Diagnosis	Palpation	Mammography	Ultrasonography	Cytology
IPC ($n = 14$)	11	8	3	9
IPC and DCIS/LCIS ($n = 6$)	5	3	2	1
IPC and invasive ($n = 3$)	3	2	—	1

IPC, intracystic papillary carcinoma; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*

Local recurrence developed in one patient, 16 months after local excision, and was managed with further excision and axillary dissection. There was no axillary node involvement and the recurrence was of IPC alone. This patient had no adjuvant treatment and remains disease-free at 12-year follow-up. There were no deaths from cancer.

Discussion

Previous reports have not established the outcome of IPC alone as this condition is commonly associated with other pathological findings such as ductal carcinoma *in situ* and invasive cancer[3–5].

In 1983, Carter *et al.*[1] recognized the excellent prognosis in seven patients with pure IPC, treated with local excision, none of whom developed recurrence after 7 years' follow-up. The current clinical management of these lesions remains variable with the potential for overtreatment. This study confirmed the excellent prognosis of pure IPC. The absence of axillary node metastases in this and other studies[1], together with the low recurrence rate after adequate surgical excision, suggests that wide local excision without axillary dissection is the treatment of choice. IPC in isolation is a variant of *in situ* cancer of the breast and the place for adjuvant radiotherapy and tamoxifen is not defined.

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Improving cytological diagnosis and surgical management of parotid adenolymphoma

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Background: The role of fine-needle aspiration cytology (FNAC) in the diagnosis and management of discrete parotid swellings remains controversial. Controlled enucleation can be appropriate with accurate preoperative diagnosis. This study (1985–1995) reviewed the role of FNAC in the diagnosis and surgical management of adenolymphoma.

Methods: Review of cytological smears by two observers concentrated on the features of infarction and squamoid metaplasia. Sensitivity, interobserver and intraobserver variation were evaluated statistically in a two-run 'blinded' analysis of 80 cytological slides from a variety of lesions.

Results: Of 222 epithelial neoplasms of the parotid, 33 were adenolymphomas. FNAC was performed before operation in 32, producing 34 slides, and a correct cytological diagnosis was made in 21 patients. Retrospective review of the 34 slides, to examine specific features of squamoid metaplasia and infarction, improved diagnostic accuracy. The reliability and reproducibility of cytodiagnosis was confirmed by analysis of interobserver and intraobserver agreement. The sensitivity was high (0·76–0·88). Controlled enucleation was performed in 12 patients and superficial parotidectomy in 11. There were no tumour recurrences.

Conclusion: Attention to the features of squamoid metaplasia and infarction improves cytological diagnosis and directs appropriate surgical management.

Paper accepted 16 July 1999

British Journal of Surgery 1999, 86, 1275–1279

Introduction

Salivary adenolymphoma continues to stimulate the interest of surgeons and pathologists[1,2]. It is generally regarded as a true neoplasm confined almost exclusively to the parotid gland. Early papers[3,4] did not deliver the impact of Warthin's definitive description in 1929[5], and his eponym remains popular in the USA[6] and elsewhere[2]. Alternatively adenolymphoma is readily understood, descriptive and enjoys popular usage[7].

In a previous report[8] the aetiology, diagnosis and management of this uncommon neoplasm were described. The role of fine-needle aspiration cytology (FNAC) in the diagnosis of parotid swellings remains controversial[9] especially for adenolymphoma. A possible explanation is that infarction can engender difficulty in cytological diagnosis. Distinctive features were first documented in surgical and cytological literature in the 1970s[10–12], but may be overlooked.

For some surgeons FNAC is a routine preoperative investigation. It allows informed patient counselling and enables the surgeon to consider management options. Other surgeons regard FNAC as an irrelevant and potentially hazardous manoeuvre which should not alter a standard surgical approach to all parotid lumps (i.e. superficial parotidectomy)[9].

This study was undertaken to reassess the reliability of FNAC in the diagnosis and management of a specific parotid tumour (adenolymphoma), concentrating on infarction and squamoid metaplasia. The performance and safety of controlled enucleation of adenolymphomas using a facial nerve stimulator as proposed previously[8] was re-evaluated.

Patients and methods

Records (1985–1995 inclusive) from the histopathology department were examined and details of all salivary gland

Table 1 Salivary gland lesions identified between 1985 and 1995 in 536 patients

	No. of lesions
Epithelial neoplasms	222
Pleomorphic salivary adenoma	138
Monomorphic adenoma	7
Adenolymphoma	33
Carcinoma	44 (11 high-grade)
Other neoplasms	8
Non-Hodgkin lymphoma	4
Soft tissue neoplasm	4
Non-neoplasms	321
Submandibular sialoadenitis	142 (77 obstructive)
Sublingual sialoadenitis	26
Parotid sialoadenitis	8
Minor salivary gland lesions	122 (19 Sjögren's syndrome)
Miscellaneous	23
Total	551

Table 2 Distribution of salivary pathology: blinded cytological slides

Epithelial neoplasms	*n*
Benign	
Pleomorphic adenoma	13
Monomorphic adenoma	3
Adenolymphoma	34
Malignant	
Carcinoma ex pleomorphic adenoma	3
Adenoid cystic carcinoma	2
Mucoepidermoid carcinoma	4
Acinic cell carcinoma	2
Papillary cystadenocarcinoma	2
Low-grade adenocarcinoma	1
High-grade squamous and adenocarcinoma	4
Non-Hodgkin lymphoma	3
Metastatic oat-cell carcinoma	3
Mesenchymal neoplasms	
Lymphangioma	1
Neurilemmoma	1
Non-neoplasms	
Myoepithelial sialoadenitis	3
Tuberculosis	1
Total	80

surgery collected (*Table 1*). Thirty-three patients with adenolymphoma were identified and cross-checked from operating theatre records. Case notes were reviewed. Histopathological slides from all excised lesions were re-examined. Eighty relabelled cytological slides from FNAC of a wide variety of parotid lesions, including the 34 slides from adenolymphomas (*Table 2*), were reviewed by two observers experienced in cytodiagnosis (A.J.W. and M.F.L.). Two 'blind' runs at an interval of 2 weeks were performed. Specimens were randomly renumbered between viewing sessions. Clinical details were not provided at any stage of this review. The initial cytology reports issued by three consultant cytopathologists were checked.

All smears were air dried and stained with May–Gruenwald Giemsa. One patient had additional wet-fixed modified Papanicolaou-stained smears.

The results are presented in two parts: the original reports issued by the cytopathology department, which were incorporated prospectively into the surgical decision making, and the later retrospective review of the smears by the two observers (observer 1 (A.J.W.) and observer 2 (M.F.L.)). Each of the above was compared with the original histopathology reports.

The sensitivity of FNAC in the diagnosis of adenolymphoma was calculated for the original cytopathology department reports and for both observers. The reliability of the retrospective review of the cytological material was assessed using the κ measure of agreement for intraobserver and interobserver reliability. The κ statistic is a superior measure of agreement, revealing the level of consensus over and above chance occurrence. A κ value of 1 represents perfect agreement whereas a value of zero implies chance agreement. Absolute definitions of interpretation of the resulting κ value are not possible but in this study values were interpreted as follows: 0·0, poor; less than 0·2, slight; 0·2 to 0·4, fair; more than 0·4 to 0·6, moderate; more than 0·6 to 0·8, substantial; more than 0·8 to 1·0, almost perfect.

Discordance between the two observers at each run was investigated using the McNemar's χ^2 test for comparison of paired proportions. Statistical analysis was carried out using the Stata statistical computer package (Release 5.0; Statacorp, College Station, Texas, USA).

Results

During the study period, 551 excised salivary lesions (from 536 patients) were submitted to the histopathology department. Of 222 epithelial neoplasms, there were 33 adenolymphomas in 32 patients (14·9 per cent of the total) and 138 pleomorphic salivary adenomas. *Table 1* shows the range of parotid pathology encountered. The mean annual referral incidence of adenolymphomas was three patients.

Clinical features and preoperative diagnosis of adenolymphoma

There were 21 men and 11 women of mean age 58 (range 32–79) years. Eighteen tumours occurred on the left, 13 on the right and one patient had bilateral synchronous tumours. A painless facial swelling characterized 24 lesions and nine patients experienced some degree of intermittent discomfort. The mean interval between onset of clinical features and presentation was 30 (range 3–480) months. A history of tobacco (mainly cigarette) smoking was obtained from 25 patients.

Fine-needle aspiration cytology

All but one tumour was assessed by FNAC. One patient yielded a smear replete with profuse normal parotid acini and ducts. FNAC missed a small (8 × 5 mm) adenolymphoma (a false-negative smear for adenolymphoma) but superficial parotidectomy was performed for a palpable mass.

In the original reports issued by the cytopathology department, an opinion diagnostic of adenolymphoma was issued in 21 of 32 cases. Three of 34 smears were graded as suspicious of malignancy because of the presence of atypical cells. Two infarcted lesions were reported as possible metastatic disease from primary squamous carcinoma and the third as a metastasis from a thyroid follicular carcinoma. This latter lesion was stroma-poor and profusely oncocytic; all three were adenolymphomas histologically. Necrotic features were noted in 15 of 34 smears and squamoid cells were present in all.

Observer 1 correctly diagnosed 28 of the 34 adenolymphomas in the first run, and 30 of 34 in the second run, producing sensitivities of 0·82 and 0·88 respectively. Observer 2 correctly diagnosed 28 of 34 adenolymphomas in the first run and 26 of 34 in the second run, producing sensitivities of 0·82 and 0·76 respectively. None of the other 46 salivary lesions was diagnosed as adenolymphoma (*Table 2*).

Intraobserver agreement was substantial for observer 1 ($\kappa = 0{\cdot}77$) and moderate for observer 2 ($\kappa = 0{\cdot}46$). Interobserver variation, comparing the two observers' diagnoses from the first and second runs, was substantial at the first run ($\kappa = 0{\cdot}80$) and moderate at the second run ($\kappa = 0{\cdot}41$). Neither observer was more likely than the other to diagnose the adenolymphoma incorrectly on either run ($\chi^2 = 0$, 1 d.f., $P = 1{\cdot}0$ for the first run; $\chi^2 = 2{\cdot}67$, 1 d.f., $P = 0{\cdot}103$ for the second run). The difference in the proportions failing to identify adenolymphoma between observer 1 and observer 2 was 0 (95 per cent confidence interval (c.i.) 11·1–11·1) per cent on the first run and 11·8 (95 per cent c.i. 28·3–4·7) per cent in favour of observer 1 on the second run.

Neither observer (*Table 2*) confirmed the initial false suspicious readings from the cytopathology department. Two important aspects of cytodiagnosis (*Figs 1* and *2*) emerged. (1) Necrotic/infarcted material from adenolymphoma is characteristic on Giemsa smears. It stains mauve and often shows epithelial 'ghost cell' outlines and degenerate lymphocytic nuclei[13]. (2) Small cohesive sheets of squamoid cells may be present, characterized by dense ovoid nuclei and faintly staining light blue cytoplasm. These are sheets of 'dark' cells from the epithelium[2] which resemble degenerate squamous malignancy. Modified Papanicolaou-stained smears revealed that the cytoplasm of these cells exhibits striking orange staining due to prekeratin.

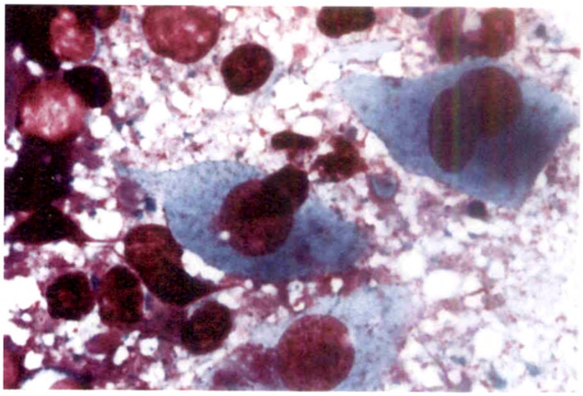

Fig. 1 Fine-needle aspiration cytology smear from a 62-year-old male smoker. Adenolymphoma deep lobe parotid showing 'light' epithelial cells accompanied by lymphocytes and characteristic background debris. (Giemsa stain, original magnification × 400)

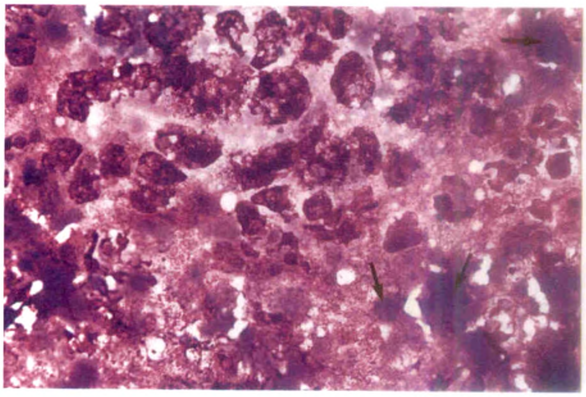

Fig. 2 Fine-needle aspiration cytology smear from a 72-year-old male smoker showing a large infarcted parotid adenolymphoma. Recognizable degenerating nuclei are present together with many discrete 'ghost cells' (arrows), an appearance typical of infarcted adenolymphoma. (Giemsa stain, original magnification × 400)

Histopathology

A detailed analysis of the histopathology from all 33 lesions confirmed a striking variability within adenolymphomas; eight demonstrated infarction and seven showed gross squamoid metaplasia.

Table 3 Surgical management

		Operations performed					
Specialty	FNAC	Controlled enucleation	Superficial parotidectomy	Local excision	Other	Total	Complications
General	24	12	7	5	0	24	2 Frey's syndrome 2 Temporary VII palsy
ENT	7	0	3	2	2*	7	0
Maxillofacial	1	0	1	1	0	2	1 Permanent VII palsy
Total	32	12	11	8	2	33	5

*One lymph node biopsy and one parotid exploration. FNAC, fine-needle aspiration cytology; ENT, ear nose and throat

Surgical treatment

General surgeons treated 23 patients (24 lesions), otolaryngological surgeons seven patients and oromaxillofacial surgeons two patients. Operations recorded were superficial parotidectomy (11), controlled enucleation (12), and ten other procedures variously described as local tumour excision (eight), parotid exploration (one) and lymph node biopsy (one). No patient with a pleomorphic or monomorphic adenoma was treated by controlled enucleation (*Table 3*).

Follow-up

Follow-up by clinic attendance ranged from 6 to 84 months and there was no instance of recurrent neoplasm. One patient with bilateral adenolymphomas removed by controlled enucleation developed a new lesion distant from the previous site, proven by FNAC, 2 years later. This tumour has remained clinically quiescent at 80 months from discovery. Annual follow-up is planned.

Complications

Eleven complications were noted, including facial nerve weakness in three patients following superficial parotidectomy; this resolved in two patients but in one partial weakness was permanent. Enucleation was not associated with any form of facial nerve weakness. Other events included Frey's syndrome in two patients (after superficial parotidectomy), a haematoma requiring evacuation, a seroma treated by repeated aspiration and minor skin necrosis in two patients.

Discussion

Clinical features may help predict whether a salivary gland swelling is benign[14] but clinical errors leading to inappropriate surgery do occur[15,16]. To distinguish adenolymphomas from other benign adenomas and some low-grade cancers is rarely possible[6,8]. Although controversial, local excision for adenolymphoma has been advocated[6,8,17,18]. Controlled enucleation as previously defined[8] was performed for 12 of 33 tumours in the present study but only by general surgeons. This operation is attended by a minimal complication rate, especially for facial nerve function and in this series was never undertaken inappropriately. Superficial parotidectomy might be regarded as a logical procedure for adenolymphoma, because of potential multicentricity[7,19], but in this series there were no recurrences and only one new tumour. FNAC can assist surgical planning for salivary disease in general and parotid lesions in particular[20,21], but a significant problem has been difficulty in cytodiagnosis; the present authors have addressed this.

Infected, otherwise necrotic or infarcted adenolymphoma, was described in 1970[10] and the cytological features reported in 1976[11]. Eveson and Cawson[12] reviewed 323 adenolymphomas from the British Salivary Gland Tumour Panel and found 20 examples (6·2 per cent) of tumours which demonstrated gross infarction and fibrosis. In the present series, eight of 33 tumours revealed some degree of infarction.

The diagnostic accuracy of FNAC from the initial cytopathology department reports had not changed since 1986[8]. There emerged, in effect, a false-positive rate of three of 32 as these smears were graded 'suspicious of malignancy'. Because the FNAC result was prospective, surgery was influenced and superficial parotidectomy performed. Other reports of false-positive FNAC smears in Warthin's tumour[22,23] emphasize this pitfall. This study suggests that specific attention to the features of infarction and squamoid metaplasia should lead to a reduction in false-positive or suspicious gradings. If cytological uncertainty persists then superficial parotidectomy is obligatory. This was performed in four of the eight infarcted adenolymphomas encountered.

The precision and clinical usefulness of FNAC has been seriously challenged[9,24,25]. The present study endeavoured to address this issue objectively in the 80 'blinded' slide examinations. This represented a wide range of salivary pathologies (*Table 2*). The cytological readings displayed a high sensitivity (0·76–0·82) and the calculated κ values demonstrated moderate to substantial reliability for intra-observer and interobserver error. The conditions operating for this 'test' were far more stringent than those in working FNAC practice where full clinical details are available. This study indicates the objectivity and reproducibility of smear diagnosis for adenolymphoma. No lesion other than adenolymphoma was diagnosed as such.

Important audit lessons also emerged from the blinded study. It confirmed recognized pitfalls in salivary cytology, for example, problems in recognizing low-grade cystic mucoepidermoid carcinoma and in distinguishing atypical pleomorphic adenoma from monomorphic adenoma and adenoid cystic carcinoma[22]. This slide set will be incorporated into departmental teaching and quality control.

Currently, cytologically proven adenolymphomas are treated by controlled enucleation with minimal morbidity. The recognition of cytological features indicating infarction and squamoid metaplasia should improve diagnostic precision and reduce the number of tumours treated by some form of parotidectomy.

Acknowledgements

The authors are indebted to many colleagues in general, otolaryngological and maxillofacial surgery for permission to study their patients' notes and include the findings in this series. Professor J. B. Bradfield kindly allowed access to the histopathology files and expert help was received from Dr J. W. Eveson. This study was supported financially by the University of Bristol.

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Emerging trends in the management of the impalpable testis

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Background: The management of the impalpable undescended testis is controversial. The study examines emerging trends in the management of this problem.

Methods: Two groups of boys were treated consecutively and recorded prospectively from 1974 to 1984 and from 1990 to 1998 inclusive. A consistent policy of using the preperitoneal approach for impalpable testis was adopted during both time intervals but during the second study period examination under anaesthesia and diagnostic laparoscopy were introduced to ascertain testicular presence and location.

Results: Some 919 boys were treated for cryptorchidism during the study period. Ninety boys in the first group (23 per cent) underwent preperitoneal explorations for impalpable testes. Anorchia was present in 18 and orchidectomy was performed in two boys. Thirty boys in the later group (5 per cent) were diagnosed as having impalpable testes. Fifteen boys underwent successful preperitoneal orchidopexy, anorchia was present in 11 and four underwent orchidectomy, carried out for high intra-abdominal testes.

Conclusion: Examination under anaesthesia and subsequent laparoscopic assessment for all impalpable testes has reduced the need for preperitoneal exploration for the impalpable undescended testis. In this large series, division of the testicular vessels in order to secure scrotal placement of the testis was required in one instance only.

Paper accepted 18 July 1999

British Journal of Surgery 1999, 86, 1280–1283

Introduction

The incidence of cryptorchidism at 3 months of age is about 1·5 per 100 male births[1]. In approximately one-fifth of these children, the testis is reported to be impalpable[2–4]. In this situation there remains much debate over the method of orchidopexy. The Fowler–Stephens procedure, in which the gonadal vessels are divided in one or two stages, is widely practised although the operation has uncertain effects on the viability of the testis, and an incidence of late atrophy of some 25 per cent[4]. Moreover, unproductive exploration of the intra-abdominal testis through a groin incision is still reported[5]. The alternative is to approach the vessels above an abdominal testis directly, and to divide under vision the fibrous bands that restrict their intrinsic elasticity. This can be achieved either by an open abdominal preperitoneal approach[6,7] or by dissection through the laparoscope[8].

The defined area of the Grampian region of Scotland is served by a single children's hospital, and over the past 25 years two surgeons have given particular attention to the management of impalpable testes. Over 900 boys have been studied prospectively. This paper records the evolving trends in the diagnosis and treatment of impalpability. In the latter half of the period, the adoption of examination under anaesthesia (EUA) and laparoscopy has produced important improvements in diagnosis, while increasing experience has provided a balanced approach to treatment.

Patients and methods

Patients

Over 900 boys who presented with undescended testes to the Royal Aberdeen Children's Hospital were studied during a 25-year period. This centre provides for a population of approximately 100 000 children. Data were collected prospectively by two surgeons working consecutively over the period 1974–1998. The patients treated by each surgeon are grouped separately: cohort 1 was treated between 1974 and 1984, and cohort 2 during 1990–1998.

Clinical methods

The preperitoneal approach was adopted for regular use over the period 1974–1984 (cohort 1), and was used whenever bedside palpation suggested that difficulty was anticipated in treating emergent or impalpable testes through an inguinal canal approach. All readily palpable testes were treated by standard Bevan orchidopexy. Neither EUA nor laparoscopy was used during this period. The method and results of this technique have been reported previously[6,7].

Introduction of laparoscopic evaluation in 1990 prompted an alternative management strategy. Hence, in the second group (cohort 2), if clinical examination revealed an impalpable testis, the child was first examined under anaesthesia, with the option of proceeding with a Bevan approach if a testis was palpated. If, however, the testis remained impalpable, laparoscopy was undertaken. Identification of an intra-abdominal testis prompted subsequent preperitoneal orchidopexy. The finding of a blind-ending vas deferens, or vas and vessels entering a closed internal ring, resulted in no further surgery, with testicular regression being the assumed clinical diagnosis[9]. The presence of vas and vessels entering an open internal ring prompted exploration through a groin approach.

The age at presentation, incidence of impalpable testis, site or absence of the testis, and the results of surgery, as well as the differing approach to diagnosis and management, were recorded in both cohorts.

Results

The number of children presenting with an abdominal testis and the incidence of bilaterality and anorchia are shown in *Table 1*.

Cohort 1

During 1974–1984, 398 operations (64 bilateral) were performed in 334 boys. Of 308 palpable testes, 235 were placed in the scrotum by the Bevan approach, and in 73 emergent testes the preperitoneal approach was used. All 308 testes were palpable in the scrotum 1 year later. Among 90 impalpable testes, all were explored through a preperitoneal approach, 18 proved to be absent, two intra-abdominal testes were removed and 70 were placed in the scrotum (28 abdominal, 42 high canalicular). One year later, 66 of the 70 were in the scrotum and 59 had grown in size. Of the 28 intra-abdominal testes, 25 were intrascrotal and of normal size[7].

Cohort 2

During 1990–1998, 585 boys presented with cryptorchidism and 574 boys underwent 703 operations (129 bilateral). At EUA, in only 30 boys did the testis prove to be impalpable. At laparoscopy anorchia was found in 11 boys. Fifteen boys underwent orchidopexy by the preperitoneal approach for intra-abdominal testis, compared with 90 in cohort 1 ($P < 0{\cdot}0001$, Yates-corrected χ^2 test). The procedure was successful in all but one boy, in whom a high intra-abdominal testis was treated by the Fowler–Stephens procedure. This was carried out in preference to orchidectomy since it was associated with testicular regression on the contralateral side. Four boys had orchidectomy performed for testes that would not reach the internal ring following complete mobilization. Six of the 555 boys who had initially undergone orchidopexy by the Bevan approach subsequently underwent revision orchidopexy because of dartos pouch failure.

Age at presentation

In spite of efforts to secure earlier referral, at no time in the 25-year period were more than 30 per cent of boys seen before the age of 3 years. The proportion of boys over 5 years of the age at first presentation did not fall below 50 per cent at any time in the study.

Discussion

It is now 100 years since Bevan described the inguinal approach for orchidopexy[10], which remains uncontested as

Table 1 Incidence of undescended and impalpable testis, abdominal testis and anorchia

				Impalpable			
Cohort	Period	Unilateral	Bilateral	Abdominal	Canalicular	Anorchia	Total
1	1974–1984	270 (81)	64 (19)	30 (9)	42 (13)	18 (5)	334
2	1990–1998	456 (78)	129 (22)	19 (3)	0 (0)	11 (2)	585

Values in parentheses are percentages

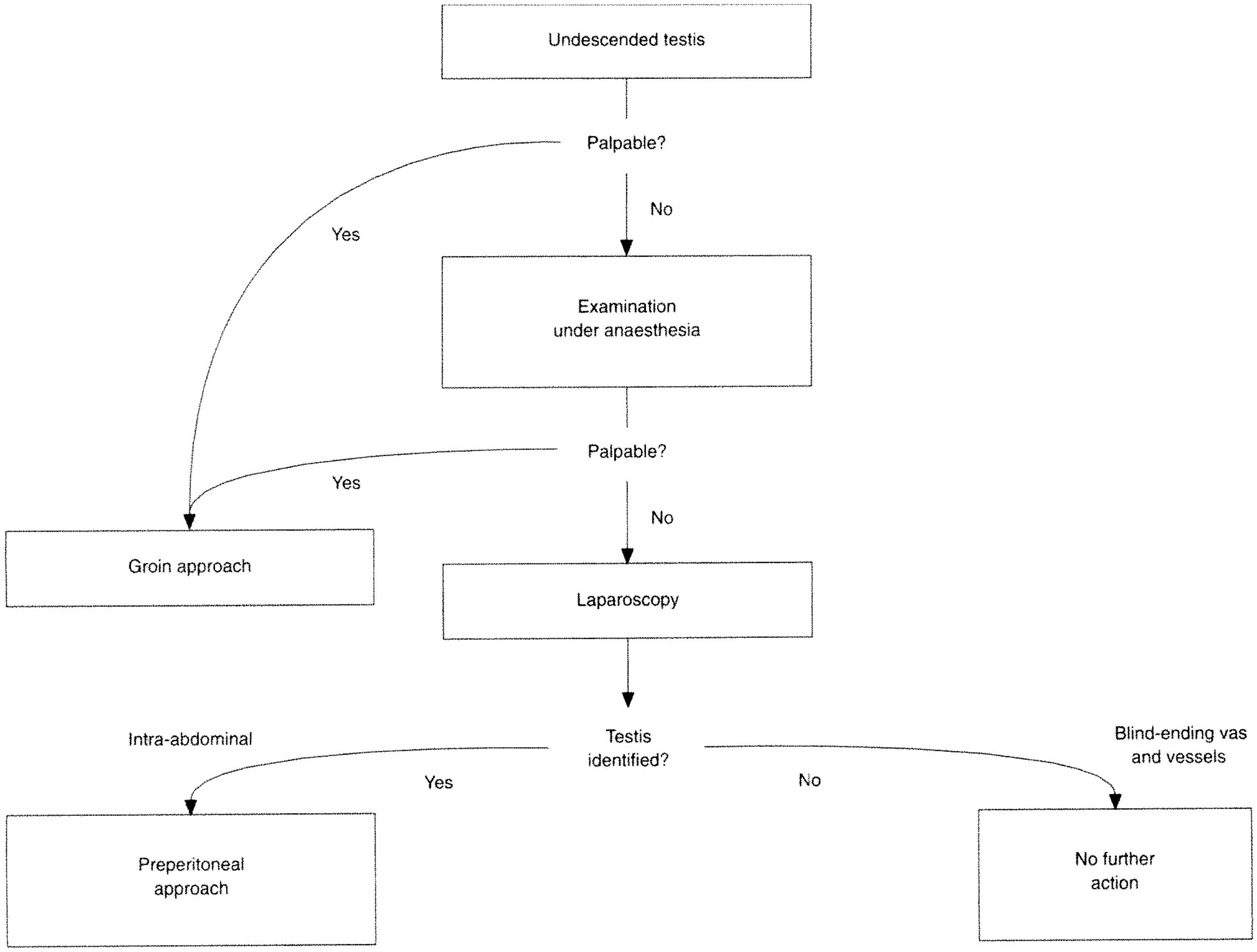

Fig. 1 Strategy for management of undescended testis

the operative route of choice when dealing with the palpable undescended testis. However, this technique is inappropriate when the testis is impalpable and hence possibly intra-abdominal, since it results in restricted access, a fact recognized by Bevan in his seminal contributions to operative care[11]. In the case of impalpable testes, one surgical option is the Fowler–Stephens procedure, which includes division of the testicular vessels, with testicular perfusion thereafter dependent upon the artery of the vas deferens[12]. This method, recently converted to a staged laparoscopic technique, is widely used but does have uncertain effects on the viability of the testis[13].

The alternative option is a direct approach to the testicular vessels with division of the fibrous bands that restrict their elasticity[14]. This can also be performed laparoscopically; however, it involves a long incision in the peritoneum, can be time consuming, and may present a late risk from adhesions[8].

The childhood population of North-East Scotland is served by the Royal Aberdeen Children's Hospital. The character of the population did not change appreciably over the 25 years of the study. Despite efforts to secure earlier referral, it is apparent that over the study period only minor changes have occurred to age at presentation. This remains a source of concern and, despite the presence of a screening programme in this region directed at early detection and referral, only 50 per cent boys of presented before reaching 5 years of age. A similar pattern is reflected in other studies[15,16].

The differences between the two study cohorts are of interest and significance. These are partly to be explained by the differences in management strategy, i.e. liberal use of the preperitoneal approach in cohort 1, and EUA and laparoscopy before orchidopexy in cohort 2 with selection of the preperitoneal route restricted to the intra-abdominal testes.

The incidence of impalpable testis in cohort 1 (23 per cent) is in line with that in other large series[2–4]. When cohort 2 was examined under anaesthesia, a testis could not be felt in 5 per cent of boys, an incidence similar to that found by others using this approach[9]. This is one of several emerging trends, which show that the following steps are important in the management of the clinically impalpable testis.

1 Impalpability must be confirmed by EUA, since testes then found to be palpable do not require a laparoscopy, and can be mobilized through the inguinal canal.
2 Laparoscopy is now established in the planning of treatment; when anorchia is confirmed, further exploration is avoided.
3 A change in the operative approach to the impalpable testis can reveal unsuspected elasticity in the testicular vessels once they are fully mobilized.

The value of this approach has been confirmed in other reports[3,4,17]. The data presented support a preferred approach to children presenting with an undescended testis (*Fig. 1*). The subjectivity of the outpatient clinic diagnosis of impalpable testis is acknowledged and the authors suggest that it is essential to identify children with a true intra-abdominal testis. EUA followed by laparoscopy achieves this and prevents the inappropriate use of the Bevan groin approach. Following identification of an intra-abdominal testis by laparoscopy, use of the preperitoneal approach, which gives the highest chance of successful placement in the scrotum whilst preserving the integrity of the vascular pedicle, is recommended.

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Experience with the preperitoneal 'plug and patch' inguinal hernia repair

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Paper accepted 4 July 1999

Introduction

The use of prosthetic material is now established in groin herniorrhaphy and the concept of 'plugging' the defect has evolved considerably since the work of Lichtenstein and Shore in 1974[1]. The mesh plug and patch hernioplasty, popularized by Robbins and Rutkow[2], relies on simplicity as well as being tension-free. The present study was an assessment of this approach.

Patients and methods

Some 175 consecutive patients (168 men; mean age 57 years) presenting to one general surgeon over 20 months with a symptomatic inguinal hernia who underwent elective surgery were included. All hernias were repaired with a Bard mesh PerFix plug (Davol, Cranston, Rhode Island, USA) (*Fig. 1*) using a standard operative technique with diathermy dissection[2]. An oblique 4–6-cm incision from the pubic tubercle was used. Indirect sacs were separated from the cord and inverted into the internal ring and the plug inserted, tapered end first (*Fig. 2*). The size of the deep ring determined the size of the plug (four are available). One or two interrupted absorbable sutures were placed as required between the petals of the plug and the margins of the ring to prevent possible migration. For direct hernias, the fascia over the defect was circumscribed near its base, and the plug was positioned in the preperitoneal plane and sutured to the edge of the defect. In both types of hernia the accompanying preshaped onlay mesh patch was placed, but not sutured, over the posterior wall.

Both general and epidural anaesthesia were employed. All patients received a single bolus of prophylactic antibiotic. Inpatients were older than those having day-case surgery (104 patients of mean age 63 years *versus* 71 of mean age 49 years). At discharge, patients were advised to return to normal activities as soon as they felt they could and the first 40 were asked to bring back a questionnaire about 'return to pain-free activities'. The first 100 patients were followed up at 4–6 weeks.

Results

There were 182 hernias repaired during this interval (seven bilateral). There were 100 indirect hernias and 14 recurrent hernias. There was no case of postoperative urinary retention. At follow-up, one patient reported having seen his own doctor for a superficial wound infection. Three patients were seen with wound haematomas (one needed drainage) and one patient developed a small scrotal seroma. Median time to pain-free walking was 4 (range 1–21) days and that for driving a car was 11 (range 1–35) days.

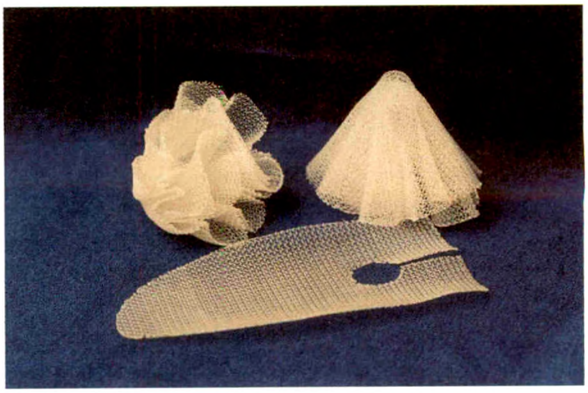

Fig. 1 The 'plug and patch' mesh

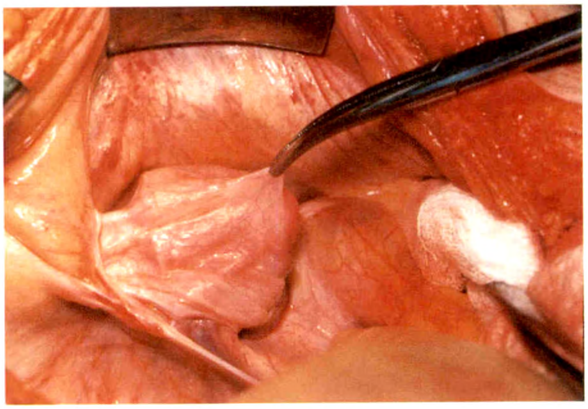

Fig. 2 Intra-abdominal view (at laparotomy) of a plug previously used to repair a right indirect inguinoscrotal hernia. Note the plug sits comfortably in the preperitoneal plane astride the defect

Discussion

At present the most common open approach to inguinal hernia repair appears to be the Lichtenstein mesh hernioplasty[1,3]. The Nyhus approach[4] (posterior preperitoneal) seems unnecessary in the majority of primary hernias. Laparoscopic hernioplasty is expensive, technically demanding and not universally applicable.

There was some initial doubt that herniorrhaphy[2] could be performed through 4–6-cm incisions but in practice the technique has a short learning curve. Patient acceptability is high, probably owing to the smaller incision and resultant diminished tissue trauma. This may also explain the low incidence of wound complications observed but, as not all of the patients were seen routinely after operation, further minor morbidity may have occurred. This technique was learned under epidural anaesthesia; repair has not been attempted under local anaesthesia as it would probably lead to intolerable discomfort from traction on the wound.

Recurrence following herniorrhaphy is clearly an important issue but cannot be commented on from this series. To date no recurrence has been observed. However, in one institution, of 3000 repairs there have been only 21 documented recurrences at a median follow-up of 5 years (I. M. Rutkow, unpublished results). As the patients are offered complimentary surgery in the event of a recurrence, this should be an accurate audit.

In summary, the PerFix plug hernioplasty combines the advantages of an open anterior approach to the preperitoneal space and a sound prosthetic repair.

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Survival of patients with colorectal cancer diagnosed in a randomized controlled trial of faecal occult blood screening

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Background: Analysis of survival of subjects with colorectal cancer diagnosed by different modalities can provide insight into the mechanism by which screening has an effect. It can also give an indication of the feasibility of using prognostic indicators as surrogate outcome measures to predict mortality in future studies.

Methods: This paper examines the survival of individuals with colorectal cancer diagnosed in the Nottingham trial and explores the role of selected prognostic factors as possible surrogate outcome measures.

Results: Survival was significantly better in subjects with screen-detected cancers than in controls, even after adjusting for tumour stage and accounting for lead-time bias. Survival was inversely related to stage of tumour, with patients with stage A tumours having the best survival. Subjects with well or moderately differentiated tumours had a significantly better survival than those with poorly differentiated tumours.

Conclusion: Screening for colorectal cancer by means of faecal occult blood testing improved survival among subjects with screen-detected cancers. Differences in prognostic factors largely explain the differences in survival between both non-responders and subjects with interval cancers and those in the control group, but not the improved prognosis for patients with screen-detected cancers. The use of such factors as surrogate outcome measures may therefore be inappropriate.

Paper accepted 28 May 1999

British Journal of Surgery 1999, 86, 1286–1291

Introduction

The Nottingham trial of faecal occult blood (FOB) screening for colorectal cancer was a randomized controlled trial in which 152 850 people aged 45–74 years were randomly allocated to a screening or control group; those in the screening group were offered FOB testing every 2 years. After a median follow-up of 7·8 years, there was a 15 per cent reduction in the mortality rate from colorectal cancer in the group offered screening[1].

Analysis of survival in screening studies is affected by a number of biases. Lead-time bias results from the fact that the date of diagnosis in screen-detected patients is advanced, thus increasing length of survival even if date of death is not affected. Length bias results from the fact that slower-growing tumours, which may be associated with improved prognosis, spend longer in the 'screen-detectable phase' and are therefore more likely to be detected by screening. Selection bias, whereby those accepting screening are at different underlying risk from non-acceptors, affects any comparisons between these two groups. The main measure of effectiveness in such studies is therefore disease-specific mortality (since any effect on all-cause mortality will be too small to observe). Nevertheless, analysis of survival of individuals with colorectal cancer diagnosed by different modalities, and the effect of stage of disease on this survival, can provide further insight into the mechanism by which screening has an effect. It can also indicate whether it may be feasible to use prognostic indicators to predict mortality with sufficient accuracy that future studies could use these as alternative or surrogate outcome measures, with the resulting advantages of earlier results and potentially smaller sample size[2].

The present paper examines the survival of subjects with colorectal cancer diagnosed in the Nottingham trial, according to the study group and method of detection.

Patients and methods

Details of the study design have been reported elsewhere[3] and are summarized here. Between February 1981 and January 1991, 152 850 individuals aged 45–74 years who lived in the Nottingham area of the UK were recruited to the study. After exclusion of individuals who had a serious illness, could not be traced or had emigrated, individuals were randomly allocated (by household) to screening (75 466) or no screening (controls; 76 384).

The date of entry to the study for all participants was set to be the date on which the first invitations for screening were sent to screening group participants in a particular general practice. Screening group participants were invited to take part in screening every 2 years.

Almost 60 per cent of subjects in the screening group completed at least one screening test. Data on subjects diagnosed with colorectal cancer during the trial fieldwork, including date of diagnosis, tumour differentiation, tumour subsite and Dukes stage, were obtained from histopathology registers of local hospitals, the Trent Regional Cancer Registry and local doctors' reports.

The present analysis includes subjects with colorectal cancer diagnosed during the 10-year period of the fieldwork of the trial. All deaths up to 31 December 1996 were included and follow-up was censored at that date. The median follow-up from diagnosis (with 25 and 75 percentiles) using the reverse Kaplan–Meier method[4] was 4·2 (1·9–6·9) years.

Colorectal cancers diagnosed in the study participants were classified as: control group ($n = 1019$) and screening group ($n = 1032$). The screening group was further classified as: (1) screen-detected, if cancer was diagnosed following a positive FOB test result, divided into those detected at first screen ($n = 104$) or a subsequent screen ($n = 132$); (2) interval cancers, if cancer was diagnosed following a negative FOB test result or after a positive result where further investigation was negative or was refused ($n = 320$); (3) non-responders, where cancer was diagnosed in a subject not previously screened ($n = 464$); and (4) adenoma follow-up, where cancer was diagnosed during endoscopic follow-up subsequent to a diagnosis of adenoma ($n = 12$).

Data were complete for each variable apart from 72 subjects with missing values for Dukes stage, 383 with missing values for tumour differentiation and 42 with missing values for tumour subsite.

Statistical analysis

Survival analysis using Kaplan–Meier and Cox proportional hazards methods was carried out using the statistical package Stata (Stata Corporation, Texas, USA). The main endpoint for analysis was death from verified colorectal cancer (903 events), which included deaths verified from patient records as definitely or probably due to colorectal cancer[1].

A suggested technique to apportion improved survival in subjects with screen-detected cancer into lead-time and true benefit is to look at survival using time since entry to the trial rather than time since diagnosis of colorectal cancer between the study and control groups[5], with year of entry and age at entry replacing year of diagnosis and age at diagnosis, respectively, in the analysis. This has also been investigated here.

Survival curves were compared assuming proportional hazards with either the log rank test, when examining binary or nominal variables, or the log rank test for trend[6], when examining ordinal variables. For the stepwise Cox regression, variables were entered using a backward elimination procedure. After checking for normality, analysis of age at diagnosis and at trial entry was carried out using unpaired t tests and one-way analysis of variance with Bonferroni multiple comparisons.

Results

Table 1 shows the distribution of tumour characteristics in the two study arms of the trial and for cancers diagnosed by different methods in individuals allocated to screening.

Colorectal cancers detected at first screen were found to have the highest percentage of stage A tumours and lowest percentage of stage 'D' tumours, with a relatively lower percentage of stage B tumours compared with all the other modes of detection. Cancers detected at later screens were also observed to have a high percentage of stage A tumours and low percentage of stage 'D' tumours. Interval cancers and non-responders had a stage distribution similar to that in the control group.

The great majority of cancers were moderately differentiated, although screen-detected cancers had a higher percentage of well differentiated and a lower percentage of poorly differentiated tumours. There was also a notably high proportion of missing data for this variable ($n = 383$; 18·7 per cent).

Among cancers detected at first screen, the highest percentage were in the sigmoid and descending colon; there appeared to be a similar distribution of tumour subsite amongst all other categories.

Table 2 shows the mean age at diagnosis by study arm, method of cancer detection and sex of individuals. Although no significant difference in age was found between individuals with cancer in the screening arm *versus* controls, a significant difference was observed according to how the cancer was detected. Subjects with cancer detected at first

Table 1 Distribution of tumour characteristics in the study population

	Screening group						
Variable	First screen	Repeat screens	Interval	Non-responder	Adenoma follow-up	Total	Control group
Dukes stage							
A	48 (46·2)	49 (37·1)	49 (15·3)	51 (11·0)	3 (25)	200 (19·4)	118 (11·6)
B	24 (23·1)	47 (35·6)	107 (33·4)	160 (34·5)	0 (0)	338 (32·8)	348 (34·2)
C	27 (26·0)	24 (18·2)	95 (29·7)	99 (21·3)	7 (58)	252 (24·4)	300 (29·4)
'D'	5 (4·8)	8 (6·1)	63 (19·7)	135 (29·1)	2 (17)	213 (20·6)	210 (20·6)
Unknown	0 (0)	4 (3·0)	6 (1·9)	19 (4·1)	0 (0)	29 (2·8)	43 (4·2)
Tumour differentiation							
Well or moderate	80 (76·9)	112 (84·8)	215 (67·2)	288 (62·1)	10 (83)	705 (68·3)	666 (65·4)
Poor	9 (8·7)	10 (7·6)	52 (16·2)	57 (12·3)	1 (8)	129 (12·5)	168 (16·5)
Unknown	15 (14·4)	10 (7·6)	53 (16·6)	119 (25·6)	1 (8)	198 (19·2)	185 (18·2)
Tumour subsite							
Rectum and rectosigmoid	28 (26·9)	50 (37·9)	108 (33·7)	193 (41·6)	6 (50)	385 (37·3)	405 (39·7)
Sigmoid and descending colon	61 (58·7)	42 (31·8)	87 (27·2)	131 (28·2)	1 (8)	322 (31·2)	294 (28·9)
Transverse and ascending colon	15 (14·4)	40 (30·3)	117 (36·6)	122 (26·3)	5 (42)	299 (29·0)	304 (29·8)
Unknown	0 (0)	0 (0)	8 (2·5)	18 (3·9)	0 (0)	26 (2·5)	16 (1·6)
Total	104 (100)	132 (100)	320 (100)	464 (100)	12 (100)	1032 (100)	1019 (100)

Values in parentheses are percentages

Table 2 Mean age at diagnosis of colorectal cancer

	Mean(s.d.) age at diagnosis (years)
Study group	
Allocated to screening	69·6(7·4)
Allocated to control	69·4(7·4)
How cancer was detected	
Screen detected	
First screen	67·0(6·7)
Subsequent screen	69·2(6·1)
Interval	69·9(8·0)
Non-responder	70·3(7·4)
Adenoma follow-up	67·2(7·7)
Sex	
M	69·0(7·3)
F	70·1(7·5)

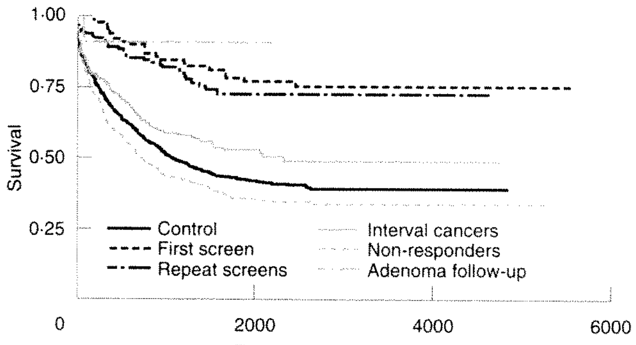
Table 3 Univariate analysis of survival following diagnosis of colorectal cancer ($n = 2051$)

	Hazard ratio
How cancer was detected	
Control group	1·0
Screen detected	
First screen	0·28 (0·18–0·42)
Subsequent screen	0·34 (0·24–0·49)
Interval	0·78 (0·64–0·96)
Non-responder	1·21 (1·04–1·41)
Adenoma follow-up	0·15 (0·02–1·06)
Dukes stage	
A	1·0
B	5·02 (3·31–7·61)
C	9·43 (6·26–14·22)
'D'	57·18 (37·73–86·64)
Unknown	20·79 (12·47–34·67)
Tumour differentiation	
Well or moderate	1·0
Poor	1·78 (1·49–2·13)
Unknown	3·33 (2·84–3·90)
Tumour subsite	
Rectum rectosigmoid	1·0
Sigmoid and descending colon	0·99 (0·84–1·16)
Transverse and ascending colon	1·25 (1·07–1·46)
Unknown	5·54 (3·63–8·46)

Values in parentheses are 95 per cent confidence intervals

screen were significantly younger than those in the control group ($P = 0{\cdot}002$), whereas patients with cancer in the non-responder group were older than the controls ($P = 0{\cdot}04$). Cancers in women were found to have been diagnosed at a significantly older age than cancers in men ($P = 0{\cdot}001$).

Table 3 shows the results of fitting a univariate survival analysis to each of the variables mentioned above, including subjects with unknown tumour characteristics. Patients with screen-detected cancers or adenoma follow-up had the best survival, although the latter group comprised only 12 individuals. Subjects with interval cancers also appeared to have better survival than those in



No. at risk			
—— 1019	167	14	–
---- 104	56	9	–
-·— 132	36	4	–
······ 320	45	3	–
- - - 464	63	11	–
·-·- 12	2	1	–

Fig. 1 Survival of subjects following diagnosis of colorectal cancer according to method of detection

the control group. The prognosis for non-responders was significantly worse than that for the control group. The survival curves, based on disease-specific mortality, are shown in *Fig. 1*.

Hazard ratios increased with increasing age at diagnosis of cancer but were significant only in subjects aged 75 years or more compared with subjects aged 54 years or less. Tumour stage and differentiation had the expected effect on survival, whereas sex, tumour subsite and year of diagnosis appeared to have no effect. Overall, the hazard ratios remained almost unchanged when analysis was carried out after excluding cases with unknown tumour variables (data not shown).

Table 4 shows the results of fitting a survival analysis using a multivariate backward procedure with a probability of removal from the model of $P = 0{\cdot}1$ on the same variables, including individuals with unknown tumour characteristics. With stage and tumour differentiation included in the model, the hazard ratio in non-responders was no longer significantly different to that of the control group. Likewise, the hazard ratio in the interval cancer group was no longer significantly lower. The inclusion of stage and tumour differentiation increased the hazard ratio for cancers detected at first screen from 0·28 to 0·53 (0·37 to 0·55 in those with known tumour characteristics only) and for cancers detected at a later screen from 0·34 to 0·62; however, these were still significantly low compared to control group cancers. Exclusion of cases with unknown tumour characteristics did not change the hazard ratios to any significant extent.

Age at diagnosis was found to have an effect on survival, with patients of older age having poorer survival.

Table 4 Multivariate analysis* of survival following diagnosis of colorectal cancer ($n = 2051$)

	Hazard ratio
How cancer was detected	
Control group	1·0
Screen detected	
First screen	0·53 (0·34–0·81)
Subsequent screen	0·62 (0·43–0·90)
Interval	0·88 (0·72–1·07)
Non-responder	1·04 (0·89–1·22)
Adenoma follow-up	0·14 (0·02–0·98)
Dukes stage	
A	1·0
B	5·11 (3·35–7·80)
C	9·41 (6·20–14·27)
'D'	45·26 (29·65–69·08)
Unknown	12·14 (7·19–20·49)
Tumour differentiation	
Well or moderate	1·0
Poor	1·29 (1·08–1·54)
Unknown	2·13 (1·78–2·56)

Values in parentheses are 95 per cent confidence intervals. *Using a backwards stepwise model with probability of removal $P = 0{\cdot}1$

However, when subjects with unknown tumour characteristics were removed from the analysis, age at diagnosis no longer had a significant effect (data not shown).

Inclusion of tumour subsite, sex and year of diagnosis made little difference to the results of the multivariate analysis. The adequacy of the final model and the assumption of proportional hazards were checked and accepted by analysing the martingale residuals[7].

Using the endpoint of verified colorectal cancer death and other deaths certified as colorectal cancer in the analysis did not dramatically change the results described above, and no significant difference in all-cause mortality was found between the two arms of the study after excluding deaths from colorectal cancer.

Analysing survival of patients with colorectal cancer using time since entry into the trial by study arm, the median follow-up from trial entry (with 25 and 75 percentiles) was 10·1 (8·6–11·9) years. Subjects with colorectal cancer in the screening group had significantly better survival ($\chi^2 = 9{\cdot}86$, 1 d.f., $P = 0{\cdot}002$). Further work will use the survival in the two groups to estimate average lead time and benefit.

Discussion

Analysis of survival by method of detection provides further insight into the means by which the benefit of screening is produced. In addition, analysis by prognostic factors gives an indication of the potential for use of these factors as surrogate outcome measures to predict mortality in future studies. The use of surrogate outcome measures has been proposed as a means of designing randomized controlled trials of screening that will provide results much earlier than trials dependent on mortality as an outcome. They may also require smaller numbers of subjects because of lower variation in the outcome measures. However, the accuracy of the mortality predictions has been questioned for a number of reasons[8], and the validity of such a design needs to be demonstrated, ideally in a setting such as the present trial in which the two outcome measures can be compared.

The results of this analysis suggest that, for colorectal cancer detected at first screen, about 35 per cent of the observed improvement in prognosis relative to that in cancers diagnosed in the control group is explained by differences in tumour stage and differentiation, the hazard ratio increasing from 0·28 to 0·53 with the inclusion of these factors. For cancers detected at later screens, about 40 per cent of the improvement is explained. The difference is likely to be due to length bias, with the first screen tending to detect a greater proportion of slow-growing tumours with better prognosis. Once these cancers have been removed, most of the improvement in prognosis in screen-detected cancers might be expected to be explained by the shift in stage and tumour differentiation. The fact that this does not occur may be due to shifts within individual categories that cannot be adjusted for, so that, for example, screen-detected stage A cancer may on average be diagnosed earlier than stage A control group cancers. This implies the need for caution in using prognostic factors to predict any future mortality reduction.

The multivariate analysis also shows that both the poor prognosis in the non-responder category and the better prognosis in the interval cancer group can be explained largely by the differences in stage at presentation, the non-responders tending to present at later stages and the interval cancers at an earlier stage relative to the control group.

In the Minnesota trial of FOB screening, in which a 33 per cent reduction in the rate of death from colorectal cancer was observed in a group offered annual screening relative to the control group, cancers diagnosed in the study groups but not detected by screening (primarily interval cancers) appeared initially to be associated with a somewhat worse prognosis than those in control groups, but at 13 years there was no difference in survival rate[9]. However, survival in the control group in the present study appears to be lower than that in the Minnesota study; this may be due to the selection of a volunteer population for the Minnesota trial.

In the Fünen study[10] the unadjusted survival rate varied by method of detection in a similar way to that in the present study.

This paper shows that subjects with screen-detected cancer have improved prognosis relative to those in the control group, even after adjustment for stage at diagnosis. Measuring survival from date of entry, which is unaffected by method of diagnosis, should remove any effect of lead time. The significantly better survival in the study group overall, as measured from date of entry, suggests that this benefit is not due simply to a lead-time effect.

Screening by FOB testing will lead to removal of adenomas as well as earlier diagnosis of cancers. It is possible that, in the future, a comparison of colorectal cancer incidence and mortality, and longer-term mortality reduction with survival of subjects with colorectal cancer, may provide some insight into the separate effect of these two components.

Acknowledgements

The authors thank Professor Jocelyn Chamberlain and Dr Veena Rodrigues for valuable contributions to the preparation of this paper. They also thank Dr Derek Coleman and Mrs Chris Mangham for assistance.

The Cancer Screening Evaluation Unit receives support from the Department of Health; the views expressed in this paper are those of the authors and not necessarily of the Department of Health. The Nottingham screening trial was funded by the Medical Research Council.

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Randomized controlled trial to examine the influence of thoracic epidural analgesia on postoperative ileus after laparoscopic sigmoid resection

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Background: The aim of the study was to evaluate whether perioperative epidural analgesia had any effect on the duration of postoperative ileus after laparoscopic sigmoid resection.

Methods: Twenty patients were randomized to surgery either with (group 1; $n = 10$) or without (group 2; $n = 10$) thoracic epidural analgesia. The major endpoint of the study was the time to the first postoperative bowel movement. Secondary endpoints were the interval until oral feeding was tolerated, incidence of postoperative vomiting, postoperative analgesic consumption use of patient-controlled analgesia (PCA) until the fourth day after operation, subjective pain perception and the incidence of epidural-related side-effects.

Results: Age, sex and American Society of Anesthesiologists classification were similar in the two groups. The first bowel movement was documented after a median of 54 (95 per cent confidence interval 32–127) h in group 1 and 77 (31–99) h in group 2 ($P = 0{\cdot}8$). Oral feeding without additional parenteral therapy was tolerated after 48 (40–64) h in group 1 and after 56 (48–64) h in group 2 ($P = 0{\cdot}6$). Postoperative vomiting occurred in two patients from each group. During epidural therapy the use of PCA was lower in group 1 (0·30 (0·19–0·96) mg morphine per kg) than in group 2 (0·56 (0·37–0·80) mg/kg) ($P < 0{\cdot}05$). Postoperative pain perception during rest and while coughing was similar in both groups. Three patients experienced reversible side-effects of epidural therapy (motor deficit, two patients; bladder dysfunction, one).

Conclusion: Perioperative thoracic epidural analgesia did not have a clinically relevant effect on the duration of postoperative ileus after laparoscopic sigmoid resection.

Paper accepted 7 June 1999

British Journal of Surgery 1999, 86, 1292–1295

Introduction

Postoperative ileus is a transient phenomenon occurring after abdominal surgery[1,2]. It is characterized by disturbed bowel motility, loss of peristaltic bowel sounds and abdominal distension. The main reason for postoperative ileus is a sympathetic reflex caused by operative trauma to the peritoneal cavity. Extensive manipulation of the intestine and mesentery, as well as prolonged surgery, may enhance this sympathetic response and lengthen postoperative ileus[1,3–5].

Thoracic epidural analgesia is thought to inhibit both the afferent and efferent loops of the sympathetic reflex arc[6–8]. Several randomized studies have shown that epidural analgesia shortens the duration of postoperative ileus after conventional abdominal surgery[8–11]. In 1995, Bardram *et al.*[12] suggested that a combination of thoracic epidural analgesia and early oral nutrition could reduce the duration of ileus after laparoscopic colonic resection to less than 48 h.

This study was a prospective randomized trial to determine whether continuous perioperative thoracic epidural analgesia could reduce the duration of ileus after laparoscopic sigmoid resection.

Patients and methods

Twenty patients scheduled for elective laparoscopic resection were included in the study. Exclusion criteria were: intestinal obstruction, intra-abdominal abscess or sepsis, infiltration of adjacent organs or a tumour diameter greater than 8 cm on computed tomography, severe obesity (body mass index above 32 kg/m^2), operative risk greater than American Society of Anesthesiologists class III and uncontrollable coagulopathy or thrombocytopenia. Patients with chronic analgesic, alcohol or drug abuse were also excluded from the study.

Study design

The study was approved by the local ethics committee. Informed consent was obtained from all patients. Mechanical bowel preparation and perioperative antibiotic administration were used similarly in both groups. On the day before surgery visual analogue scores for pain during rest and while coughing were assessed and the patient-controlled analgesia (PCA) device was explained to the patients. All patients were treated by the same anaesthetic team. In group 1, before induction of general anaesthesia, a thoracic epidural catheter (18-G; Portex, London, UK) was inserted between T9 and T12. The catheter was positioned using the 'loss of resistance' technique in the epidural space. An intrathecal position was excluded by a bolus injection of 3 ml bupivacaine 0·5 per cent (Carbostesin; Astra Chemicals, Wedel, Germany). Ropivacaine 0·2 per cent (Naropin; Astra Chemicals) was then administered continuously at 6–12 ml/h during surgery. In both groups anaesthesia with endotracheal intubation was performed using a standard technique with fentanyl, isoflurane and cisatracurium. Intraoperative fentanyl requirements (in micrograms) were documented for both groups.

Operative technique

All procedures were performed by an experienced laparoscopic team using a standard five-trocar technique[13]. In sigmoid colectomy for cancer, high ligation of the inferior mesenteric artery was accomplished with a linear endoscopic stapling device. After resection, the specimen was retrieved using an impermeable endoscopic bag through a minilaparotomy of approximately 3–4 cm in the left lower abdomen. The anvil of a circular stapling device was inserted into the descending colon extracorporeally. Then the minilaparotomy was closed, the pneumoperitoneum was re-established and colorectal anastomosis was completed by the 'double-stapling' technique.

Postoperative treatment

In group 1, epidural analgesia was continued after operation with 6–12 ml/h ropivacaine 0·2 per cent until 14.00 hours on the second day after operation. The efficacy of thoracic epidural analgesia was checked every 8 h by an experienced anaesthetist. All patients received supplemental PCA with morphine sulphate (MSI; Mundipharma, Limburg, Germany) until the morning of the fourth day. Thereafter oral tramadol (Tramal; Grünenthal, Stolberg, Germany) was given until discharge. Pain was assessed using a visual analogue scale at rest and while coughing. The PCA bolus was increased when the visual analogue score at rest was higher than 50. The nasogastric tube was removed at the end of the operation; intraperitoneal drains were removed on the first day after operation, at which time all patients were mobilized.

All patients received hypocaloric intravenous nutrition on the day of operation. Oral feeding was commenced with liquids on the morning of the first day after operation, and was advanced to mashed food on the second day and to regular hospital diet on day 3. Intravenous fluids were administered after the second day only if nausea or vomiting occurred. In patients who reported hiccups, heartburn or abdominal fullness, oral feeding was returned to the stage that had been tolerated before. All patients received two daily oral doses of cisapride 20 mg and methimazole 500 mg three times a day from the morning of the day after operation.

All patients were examined with respect to the major and minor study endpoints three times a day (06.00, 14.00 and 22.00 hours) until the third day after operation, twice a day from day 4 to day 6 (08.00 and 20.00 hours) and once a day thereafter (08.00 hours). Patients were asked about nausea and vomiting, and the time intervals from operation to the first flatus and the first bowel movement were recorded.

Statistical analysis

All continuous data were recorded as median (95 per cent confidence interval) and were compared between groups using the Mann–Whitney *U* test. Categorical data were compared using Fisher's exact test. $P < 0.05$ was considered significant. Statistical analysis of all data was performed using SAS for Windows 6.10 (SAS Institute, Cary, North Carolina, USA).

Results

From 1 December 1996 to 11 November 1997, 20 patients were included in the study and randomized to laparoscopic sigmoid resection with (group 1; $n = 10$) or without (group 2; $n = 10$) perioperative thoracic epidural analgesia. Age, sex, body mass index, operative time and indication for resection were comparable in the two groups (*Table 1*). The requirement for intraoperative fentanyl was significantly lower in group 1 (225 (130–230) µg) than in group 2 (575 (350–

650) μg) ($P < 0\cdot01$). There were no intraoperative or postoperative complications.

Patients in group 1 required significantly less morphine than patients in group 2 while the thoracic epidural analgesia was continued, but the total postoperative analgesic requirements were comparable in both groups up to the fourth day after operation (*Table 2*). Visual analogue scores for pain at rest or while coughing were similar in the two groups during the first week (*Table 2*).

There was no clinically relevant difference in the interval from surgery to the first bowel movement between the two groups (group 1, 54 (32–127) h; group 2, 77 (31–99) h; $P = 0\cdot8$). Vomiting occurred in two patients in each group on the first day after operation but reinsertion of a nasogastric tube was not required and oral feeding with mashed food was achieved within 3 days in all patients (group 1, 48 (40–64) h; group 2, 56 (48–64) h; $P = 0\cdot6$). A motor block of the legs was observed in two patients and urinary retention occurred in one patient from group 1. The side-effects of thoracic epidural analgesia disappeared after the ropivacaine dose was reduced but mobilization of the two patients was delayed by the motor block and a transurethral catheter had to be reintroduced in the third patient. There were no neurological symptoms in group 2. Patients with epidural therapy were discharged after 10 (8–11) days and patients without thoracic epidural analgesia 8 (8–9) days after operation ($P = 0\cdot3$).

Table 1 Clinical details in patients undergoing laparoscopic sigmoid resection with or without epidural therapy

	Group 1 (epidural) (n = 10)	Group 2 (no epidural) (n = 10)	P
Age (years)	60 (57–72)	65 (47–81)	0·9*
Body mass index (kg/m^2)	24·8 (21·8–27·1)	26·9 (21·0–28·4)	0·3*
Sex			0·6†
Men	4	2	
Women	6	8	
Indication			0·7†
Diverticular disease	3	4	
Carcinoma	7	6	
Operative time (min)	193 (130–230)	205 (180–260)	0·3*

Values are median (95 per cent confidence interval). *Mann–Whitney *U* test; †Fisher's exact test

Discussion

The positive effect of perioperative epidural analgesia on the duration of postoperative ileus after conventional abdominal surgery has been demonstrated in several prospective randomized investigations. Scheinin *et al.*[14] showed that the time interval from surgery to the first bowel movement was decreased by about 24 h when continuous epidural bupivacaine infusion was given compared with intramuscular or epidural morphine. In other prospective randomized trials, epidural bupivacaine decreased the interval from elective conventional colorectal resection to the first bowel movement by 24–99 h[8,11].

The effect of the laparoscopic technique in reducing the duration of postoperative ileus after colorectal resection has also been proven in two prospective randomized trials. Lacy *et al.*[15] found a reduced time to first flatus (mean(s.d.) 35·5(15·7) h) and tolerance of oral fluids (50·9(20·0) h) after laparoscopic compared with conventional colorectal resection (71·1(33·6) and 98·8(48·6) h respectively). In the authors' institution the first bowel movement occurred 70(32) h after laparoscopic and 91(22) h after conventional

Table 2 Postoperative analgesic consumption and visual analogue pain scores in patients undergoing laparoscopic sigmoid resection with or without epidural therapy

	Group 1 (epidural) (n = 10)	Group 2 (no epidural) (n = 10)	P*
Analgesic requirement (mg morphine per kg)			
Surgery to day 2 (during epidural)	0·30 (0·19–0·96)	0·56 (0·37–0·80)	0·04
Day 2 to day 4 (after epidural)	0·03 (0·00–0·22)	0·05 (0·00–0·28)	1·00
Surgery to day 4 (total)	0·39 (0·30–0·91)	0·62 (0·38–1·27)	0·2
Cumulative visual analogue score for pain at rest			
Surgery to day 2 (during epidural)	81 (40–109)	53 (8–110)	0·5
Day 2 to day 4 (after epidural)	21 (0–48)	10 (0–97)	0·8
Cumulative visual analogue score for pain while coughing			
Surgery to day 2 (during epidural)	227 (131–293)	215 (169–289)	0·8
Day 2 to day 4 (after epidural)	101 (64–187)	112 (51–172)	1·0

Values are median (95 per cent confidence interval). *Mann–Whitney *U* test colorectal resection[16]. Patients who had laparoscopic surgery tolerated oral feeding after a mean of 3·3(0·7) days as opposed to 5·0(1·5) days in the conventionally treated group.

Bardram *et al.*[12] suggested that the combination of laparoscopic techniques, perioperative continuous thoracic epidural analgesia with bupivacaine and early oral feeding reduces the duration of postoperative ileus to less than 48 h. Six of their eight patients first passed faeces on day 1 after laparoscopic right colectomy and a further two patients on day 2. Stimulated by these excellent results, a controlled randomized trial was done to evaluate the influence of thoracic epidural analgesia on the duration of postoperative ileus after sigmoid resection. It was not possible to reproduce the findings of Bardram *et al.*[12]. The postoperative interval to the first bowel movement was not influenced by thoracic epidural analgesia. Pain perception at rest and while coughing were comparable, and the incidence of vomiting and the interval until oral feeding were similar in both groups. The only advantage of continuous thoracic epidural analgesia after laparoscopic sigmoid resection was a lower postoperative morphine consumption. However, three of ten patients with thoracic epidural analgesia experienced side-effects of the epidural blockade, an incidence also found in other studies[17–19].

Although a minor effect of thoracic epidural analgesia on the duration of postoperative ileus may not have been detected by this small trial, the size of potential benefit does not justify the efforts associated with thoracic epidural analgesia.

Acknowledgements

The authors thank the Department of Anaesthesia for technical performance of the thoracic epidural catheter and intraoperative analgesia.

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Early ascorbic acid depletion is related to the severity of acute pancreatitis

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Background: Ascorbic acid (AA) is an important endogenous antioxidant in plasma and has been shown to be decreased at the time of hospital admission in patients with acute pancreatitis. The aim of this study was to determine whether plasma AA concentration continues to decrease after admission and whether the extent of decrease is related to the severity of pancreatitis.
Methods: Consecutive patients with mild ($n = 62$) and severe ($n = 23$) acute pancreatitis had plasma AA concentration measured on the day of recruitment and on days 2 and 5 by high-performance liquid chromatography.
Results: The plasma AA concentration in patients with acute pancreatitis was significantly less than that in normal volunteers on days 0, 2 and 5 ($P < 0{\cdot}0001$) and this was more marked in those with severe disease. There was a decrease in plasma AA concentration from day 0 to day 2 in patients with mild ($P < 0{\cdot}0001$) and severe ($P = 0{\cdot}0005$) pancreatitis, and from day 2 to day 5 in patients with severe pancreatitis ($P = 0{\cdot}023$).
Conclusion: Endogenous plasma AA continues to decrease over the first 5 days in hospital and the extent is related to the severity of acute pancreatitis.

Presented to a meeting of the Australasian Surgical Research Society, Auckland, New Zealand, August 1995 and published in abstract form as *Aust NZ J Surg* 1996, **66**: 243
Paper accepted 31 March 1999
British Journal of Surgery 1999, **86**, 1296–1301

Introduction

The management of acute pancreatitis is difficult because the key steps in its pathogenesis are not well understood. Experimental[1–4] and clinical[5,6] studies have provided some support for the concept that oxidative stress is the common pathway for the initiation of acute pancreatitis. Oxidative stress occurs when there is an imbalance between pro-oxidant activity and endogenous antioxidant defences. The most abundant endogenous antioxidant in the aqueous phase is ascorbic acid (AA) which is the bioactive form of vitamin C. Two studies of acute pancreatitis demonstrated that plasma AA was significantly below normal by the time patients were admitted to hospital, and that this fall was greater in acute pancreatitis than in other causes of acute abdomen[5,7].

This study was undertaken to determine whether plasma AA concentration continues to decrease after admission and whether the extent of decrease is related to the severity of pancreatitis.

Patients and methods

Consecutive patients admitted to Auckland Hospital with a diagnosis of acute pancreatitis were recruited over an 18-month period. The diagnosis of acute pancreatitis was based on a serum amylase level greater than 1000 units/l (Phadebas; Pharmacia Diagnostics, Uppsala, Sweden; upper limit of normal 300 units/l) in association with typical abdominal pain. Written informed consent was obtained and the study was approved by the Northern Regional Health Authority Ethics Committee. Patients were excluded from this analysis if the pancreatitis was associated with pancreatic cancer or other major intercurrent illness.

The patients were divided into mild and severe pancreatitis groups, based on their actual clinical outcome, as

Table 1 Patient demographics, aetiology, duration of pain and severity at time of recruitment

	Mild (*n*=62)	Severe (*n*=23)	*P*
Age (years)*	54 (20–96)	64 (16–85)	0·08§
Sex ratio (M: F)	29:33	15:8	0·15¶
Aetiology of pancreatitis			0·34**
Gallstones	37	11	
Alcohol	6	2	
Following ERCP	7	2	
Other	12	8	
Duration of pain (h)*†	21 (6–100)	27 (10–670)	0·01§
Predicted severity‡	1 (0–6)	4 (2–7)	<0·001§
APACHE II at recruitment	5 (0–17)	11 (1–27)	<0·001§
Organ Failure Score at recruitment	1 (0–6)	3 (0–10)	<0·001§
CRP			
Day 0	28 (1–445)	75 (7–336)	0·007§
Day 2	71 (2–308)	242 (42–396)	<0·001§
Day 5	48 (3–316)	161 (35–403)	<0·001§

*Values are median (range). †Between onset of pain and recruitment; ‡number of modified Glasgow criteria[9]. ERCP, endoscopic retrograde cholangiopancreatography; APACHE, Acute Physiology And Chronic Health Evaluation; CRP, C-reactive protein. §Mann–Whitney *U* test; ¶Fisher's exact test; **Fisher's exact test (gallstones *versus* all other causes)

defined by the Atlanta classification[8]. The predicted severity of disease on admission was determined by the modified Glasgow criteria[9], and the severity was monitored on a daily basis using the Acute Physiology And Chronic Health Evaluation (APACHE) II score[10] and the Organ Failure Score[11]. Computed tomography (CT) was performed as indicated clinically. All patients received intravenous fluids. One patient with mild pancreatitis and six with severe pancreatitis received intravenous nutrition, which contained 0·6 mmol (100 mg) parenteral vitamin C per day, during the 5-day study. No patient received enteral nutrition during the study.

Peripheral blood samples were taken from the fasting patients on recruitment (day 0) and on the morning of days 2 and 5. The blood was transported in heparinized tubes for immediate centrifugation and the plasma was stored at −80°C for subsequent analysis. AA was measured by high-pressure liquid chromatography (Walters 600E; Millipore, Medford, Massachusetts, USA) using a C18 reverse-phase column (octadecyl silane 5 μm, 220 × 4·6 mm) with an electro-chemical detector (Phillips Pye Unicam PU4022; Unicam, Cambridge, UK)[12]. This assay measures only reduced ascorbate. The smallest peaks measured were at least twice the average background fluctuation, and varied between 0·3 and 1·0 μmol/l from day to day. Concentrations below 1 μmol/l were classified as not detectable. Duplicates measured in the same run varied by 5 ± 4 per cent ($n = 14$). The intra-assay coefficient of variation for a plasma sample containing 60 μmol ascorbate was 3·9 per cent. The normal values for plasma AA were determined from 25 healthy volunteers (16 men, nine women; median age 32 (range 21–52) years) following an overnight fast. These volunteers were younger than the patients, but there is no evidence that plasma AA concentration varies significantly with age.

Random urine samples were collected at the same time as the blood samples from 15 of the healthy volunteers and 17 of the patients to determine urinary AA loss. Serum and urine creatinine were measured to correct for dilution. The ratio of serum to urinary concentration was used as the dilution fraction.

C-reactive protein (CRP) was measured by the hospital laboratory using a latex agglutination nephelometry method (Behring Diagnostics, Frankfurt, Germany).

Statistical analysis was performed using Fisher's exact test for categorical data and the Mann–Whitney *U* test for continuous and ordinal data. The Mann–Whitney *U* test was used to compare the same time points between the two groups, and the non-parametric Wilcoxon matched-pairs signed rank test was used to compare different time points within the same group. $P < 0{\cdot}05$ was accepted as significant.

Results

There were 85 patients (44 men, 41 women; median age 56 range (16–96) years) recruited for this study, of whom 62 had mild and 23 severe pancreatitis.

Six additional patients were excluded from this analysis because of pancreatic cancer ($n = 4$), biliary peritonitis ($n = 1$) and renal transplant rejection ($n = 1$). Twelve patients with mild acute pancreatitis were discharged and three with severe acute pancreatitis died within the 5-day study period. These patients did not have measurements on day 5.

Table 2 Clinical outcome of patients with acute pancreatitis

	Mild ($n=62$)	Severe ($n=23$)	P
Death	0	7	< 0·0001‡
Hospital stay (days)*	6 (2–18)	25 (2–150)	< 0·0001§
ICU stay (days)*†	–	28 (3–50)	
Organ dysfunction			
Jaundice	26	18	0·003‡
Renal	5	4	0·25‡
Respiratory	3	21	< 0·0001‡
Shock	0	10	< 0·0001‡
Coagulation	1	5	0·005†
Central nervous system	0	11	< 0·0001‡
Pancreatic complications			
Pseudocyst	0	3	0·02‡
Sterile necrosis	0	2	0·07‡
Infected necrosis	0	9	< 0·0001‡

* Values are median (range). †In the ten patients admitted to the intensive care unit (ICU). Organ dysfunction was assessed as defined in the Organ Failure Score[11]: jaundice, bilirubin > 32 µmol/l; renal, creatinine > 0·17 mmol/l; respiratory, arterial partial pressure of oxygen/fraction inspired oxygen < 300 (equivalent to partial pressure of oxygen of < 63 mmHg breathing air); shock, inotrope infusion required or systemic blood pressure < 90 mmHg and heart rate > 100 beats/min after 2 litres of intravenous fluids; coagulation, platelet count < 80 × 10^9 per litre; central nervous system, Glasgow Coma Score < 13; ‡ Fisher's exact test; § Mann–Whitney *U* test

Patients were recruited a median of 7 (range – 4 to 30) h after formal admission to hospital, excluding the five who were already inpatients.

There were no significant differences between these patient groups for age, sex distribution or aetiology of pancreatitis (*Table 1*). Nine of the 23 patients with severe pancreatitis and one with mild disease were referred from another hospital, which accounts for the significantly longer duration of pain before admission in the severe group. When these patients were excluded there was no longer a significant difference ($P = 0{\cdot}77$) in the interval from the initial onset of symptoms to recruitment into the study between mild and severe groups. The two patient groups were significantly different in terms of the predicted severity (as defined by the number of positive criteria from the modified Glasgow score), the actual severity of pancreatitis (APACHE II and Organ Failure Score) and plasma CRP level (*Table 1*).

Nineteen patients with severe pancreatitis and 17 with mild pancreatitis had CT. Patients with mild pancreatitis received intravenous fluids for a median of 3 (range 1–13) days compared with 21 (range 2–106) days for patients with severe pancreatitis. Patients with mild pancreatitis resumed eating at a median of 4 (range 1–8) days compared with 37 (range 3–103) days for the 16 patients who survived the attack of severe pancreatitis.

The clinical outcome of the patients is summarized in *Table 2*. Seven patients with severe pancreatitis died. Two of the ten patients admitted to the intensive care unit (ICU) died, one after 38 days in the unit (following prolonged sepsis of multiple organ failure) and one later on the ward from pneumonia after 85 days in hospital. Four additional patients were not expected to survive and declined admission to the ICU. Three of these patients died from respiratory failure (days 2, 3 and 8) and the fourth patient died from multiple organ failure on day 10. The remaining death occurred on the ward on day 3 from a myocardial infarction in a patient with pre-existing unstable angina. Patients with severe pancreatitis stayed in hospital significantly longer and developed significantly more organ dysfunction than those with mild disease (*Table 2*).

The median plasma AA concentration of the 25 healthy volunteers was 59 (range 27–120) µmol/l (*Fig. 1*). By comparison, the patients had persistently and significantly lower plasma AA concentrations on days 0, 2 and 5 ($P < 0{\cdot}0001$). On days 2 and 5 the patients with severe pancreatitis had significantly lower plasma AA concentrations than those with mild pancreatitis ($P < 0{\cdot}001$). There was no significant overall difference between mild and severe pancreatitis on day 0.

There was a significant decrease in plasma AA concentration from day 0 to day 2 in patients with mild ($P < 0{\cdot}0001$) and severe ($P = 0{\cdot}0005$) pancreatitis. A further decrease occurred from day 2 to day 5 in patients with severe pancreatitis ($P = 0{\cdot}023$) but not for mild pancreatitis ($P = 0{\cdot}85$). These findings were not altered when eight patients with pancreatitis who were admitted from other institutions were excluded from the analysis.

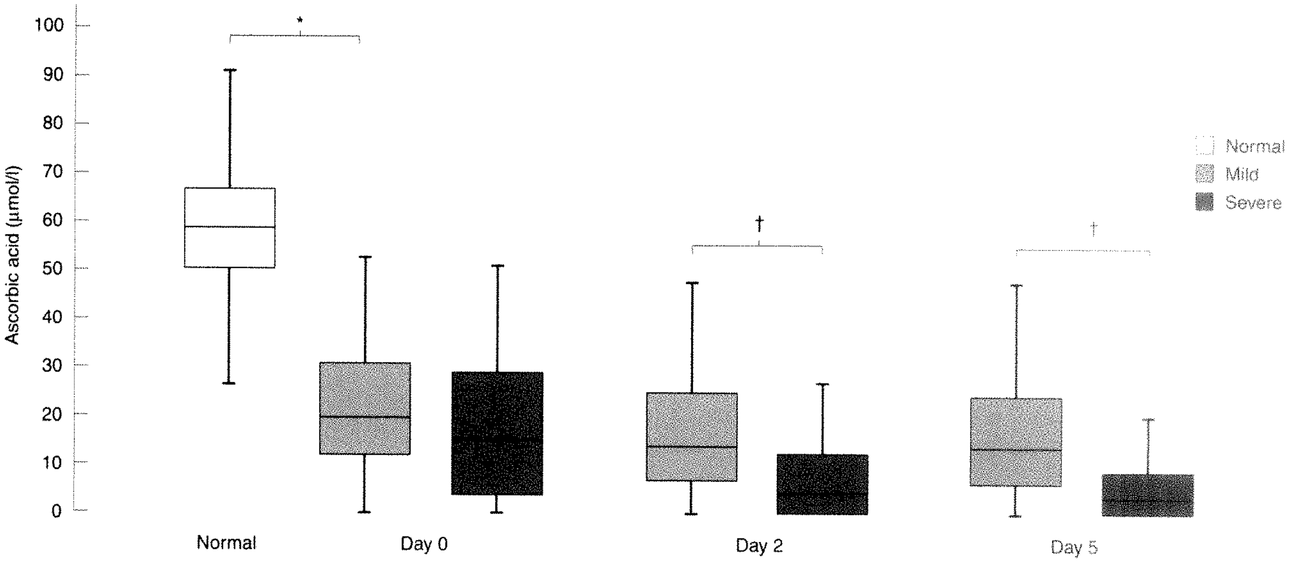

Fig. 1 Plasma ascorbic acid concentration on days 0, 2 and 5 in patients with mild and severe acute pancreatitis, and in healthy volunteers. Results are expressed as a box plot showing median (horizontal line) and interquartile range (box). The whiskers extend to the highest and lowest values within one and a half times the interquartile range from the median. $^*P < 0·0001$; $^\dagger P < 0·001$ (Mann–Whitney *U* test)

Table 3 Urinary ascorbic acid concentration corrected by the ratio of urine to serum creatinine in healthy volunteers and patients with mild and severe pancreatitis

	n	Urinary ascorbic acid (μmol/l)	*P*
Healthy volunteers	15	0·57 (0·13–13·7)	
Mild pancreatitis			
Day 0	12	0·91 (0·00–4·58)	0·83
Day 5	6	0·13 (0·09–0·53)	0·02
Severe pancreatitis			
Day 0	5	0·25 (0·00–4·50)	0·45
Day 5	5	0·26 (0·16–0·70)	0·35

Values are median (range). None of the four patient groups was significantly different from volunteers (Mann–Whitney *U* test with Bonferroni correction)

The plasma AA concentration was negatively correlated with CRP on days 0, 2 and 5 ($P = 0·02$, $P = 0·002$ and $P = 0·004$ respectively, Spearman's ρ).

The above analyses were also performed after excluding the 14 patients (six mild and eight severe) who presented more than 48 h after the onset of abdominal pain. There was no longer a significant difference between patients with mild and severe pancreatitis on days 0 ($P = 0·9$, Mann-Whitney *U* test) and 2 ($P = 0·07$, Mann-Whitney *U* test), although it was significant on day 5 ($P = 0·008$, Mann-Whitney *U* test). Analysis of the trends over the 5 days revealed a significant decrease in plasma AA concentration from day 0 to 2 in patients with mild ($P < 0·0001$, Wilcoxon test) and severe ($P < 0·005$, Wilcoxon test) pancreatitis. A further significant decrease in plasma AA concentration occurred from day 2 to 5 in patients with severe pancreatitis ($P = 0·017$, Wilcoxon test) but not in mild pancreatitis ($P = 0·8$, Wilcoxon test).

Urinary AA concentration was measured on days 0 and 5 in 17 patients (12 mild, five severe) and 15 healthy volunteers, and corrected for dilution by measurement of serum and urine creatinine (*Table 3*). There was no significant difference between healthy volunteers and patients with mild or severe pancreatitis. The corrected urine AA concentration correlated with the plasma AA concentration ($P < 0·001$, Spearman's ρ).

Discussion

This study demonstrates that plasma AA concentration was significantly below normal in patients with acute pancreatitis at the time of admission to hospital, that these low levels continued to fall after admission and that the levels were lowest in patients with severe disease. After excluding patients with prolonged symptoms, the initial values were similar in mild and severe disease, although the decrease was greater by day 5 in patients with severe pancreatitis.

The early events in the pathogenesis of acute pancreatitis are not well understood, but the uniformity of the histopathological appearances in the face of different aetiologies suggests a common pathway. Oxidative stress has been proposed as this pathway[1–5,13] and occurs when there is an increase in pro-oxidant activity in relation to endogenous antioxidant defences. AA is the bioactive form of vitamin C and a potent endogenous aqueous antioxidant which scavenges oxygen-derived free radicals produced by activated neutrophils and the hypoxanthine–xanthine oxidase system[14]. The findings of this study support the proposal that significant oxidative stress occurs early in acute pancreatitis. Other evidence for early oxidative stress comes from the finding that manganese superoxide dismutase, a mitochondrial antioxidant enzyme and a marker of myocardial ischaemia–reperfusion injury[15], was significantly raised in serum of patients with severe acute pancreatitis[16]. The pancreas is particularly prone to ischaemia[17] and it has been shown that patients with severe pancreatitis who had significant gastric intramucosal ischaemia, as measured by tonometry, were more likely to die[18].

Scott *et al.*[7] have reported low levels of plasma AA in patients with acute pancreatitis at the time of admission to hospital. They measured both plasma AA and total vitamin C and included a group of patients who were admitted with other causes of acute abdominal pain. The ratio of AA to vitamin C was strikingly different between normal subjects (80 per cent, $n = 30$), patients with acute abdominal pain (62 per cent, $n = 27$) and those with acute pancreatitis (less than 17 per cent, $n = 29$). This suggests that patients with acute pancreatitis are subject to greater oxidative stress.

There are two other possible explanations for the depletion of plasma AA. Patients might have developed acute pancreatitis because of a pre-existing decreased concentration of plasma AA. There are no reasons to suspect this to be the case and the population study required to investigate this would be prohibitively large. Alternatively patients with acute pancreatitis might have increased urinary AA losses. Urinary vitamin C levels have been measured after surgery, but not following acute pancreatitis. Crandon *et al.*[19] measured increased urinary vitamin C concentrations in nine patients after operation, but these patients had received intraoperative intravenous vitamin C. In contrast, Mason *et al.*[20] found that 24-h urinary excretion of vitamin C was lowest on the first day after operation and that it returned to normal over 8 days. Vallance[21] suggested that the mean 33 per cent fall in plasma total vitamin C levels measured on the first day after major surgery was due to increased urinary excretion. The data derived from the measurement of urinary AA concentration in patients with mild and severe pancreatitis in the present study (*Table 3*) suggest that the depletion of plasma AA cannot be explained by increased urinary losses. The significant correlation indicates that those with higher serum levels tend to have higher urine levels. There is a wide range of urinary AA levels in patients and volunteers, which means that a type II error is possible with the small number of subjects.

It is not possible to determine, from this or other studies, whether oxidative stress causes acute pancreatitis or whether it is an effect of it, predisposes to it or is just an epiphenomenon. Regardless of this, the fact that the profound depletion of plasma AA persists for some days suggests that a clinical trial investigating the impact of treatment with AA on oxidative stress and clinical outcome is justified[5]

Acknowledgements

This work was supported by the Auckland Medical Research Foundation, the Maurice & Phyllis Paykel Trust, and the Health Research Council of New Zealand. M.J.D.B. was supported by a Ruth Spencer Medical Research Fellowship. The authors thank Karen Silvers for performing the measurements of urinary ascorbic acid.

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Original article

High early mortality rate from acute pancreatitis in Scotland, 1984–1995

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Background: Death from acute pancreatitis within the first week after admission is usually a consequence of multiple organ dysfunction. Reports from specialist centres suggest that, with improvements in resuscitation and supportive care, such deaths are becoming uncommon but it is unclear if this is reflected in a decrease in early mortality rate from acute pancreatitis in the general population.
Methods: Data concerning patients discharged with a diagnosis of acute pancreatitis (International Classification of Disease-9 code 577·0) between 1984 and 1995 were obtained from the Information and Statistics Division, National Health Service in Scotland, and analysed on a computer database.
Results: The incidence of acute pancreatitis in Scotland continues to increase in both sexes. The in-hospital mortality rate (death from all causes) was 7·5 per cent and showed a slight but significant downward trend over the period of study. Death within 7 days of hospital admission accounted for 53·7 per cent of all deaths and the proportion of early deaths did not decline over the study interval.
Conclusion: These results suggest that scope remains for considerable improvement in the early management of acute pancreatitis. There is an urgent need to improve the early recognition of severe pancreatitis coupled to a willingness on behalf of clinicians to transfer these patients at an early stage to a centre with high-dependency and intensive care facilities supervised by a multidisciplinary team with expertise in the endoscopic, radiological and surgical management of these patients.

Paper accepted 14 June 1999

British Journal of Surgery 1999, **86**, 1302–1305

Introduction

Patients with severe acute pancreatitis commonly develop systemic inflammatory response syndrome within the first days of admission to hospital, characterized by a combination of pyrexia, tachycardia, tachypnoea and leucocytosis. Although resolution within 7 days is the normal outcome, a proportion of patients develop multiple organ dysfunction syndrome (MODS) in which normal homoeostatic mechanisms break down and organ failure results. The most common manifestation of this is respiratory insufficiency which affects up to 45 per cent of patients[1]. Death within the first week of acute pancreatitis is usually a consequence of MODS; reports from the early 1980s suggested that this complication accounted for around 60 per cent of such deaths[2,3]. With improvements in supportive care and increased awareness of the need for high-volume fluid resuscitation, it has been suggested that early deaths from organ failure are becoming less common[4–6]. Recent prospective studies report 30–40 per cent of deaths occurring within the first week of illness[4,7,8] but, as there are no comparative data, it has not been possible to assess the trend in early deaths over the past decade in a defined population.

Deaths in the later stages of acute pancreatitis are also associated with MODS, but after the first week of illness this is usually a manifestation of infected pancreatic necrosis. It is this complication which now accounts for the majority of deaths in specialist centres[5,6,9] but it is possible that many patients die before transfer and that reports may underestimate the number of patients dying from early organ failure. The aim of the present study was to assess the pattern of early deaths associated with acute pancreatitis in Scotland over a 12-year period from 1984 to 1995.

Materials and methods

Since 1961, National Health Service (NHS) hospitals in Scotland have been obliged to return a standard form (the Scottish Morbidity Record, SMR-1) for all patients, on which the discharge diagnosis is recorded in coded format. Data regarding admissions for all patients with a diagnosis of acute pancreatitis (International Classification of Disease-9 code 577·0) for the time period 1 January 1984 to 31 December 1995 were obtained from the Information and Statistics Division, NHS in Scotland.

In-hospital death was defined as death recorded on the date of hospital discharge. Early deaths were defined as those occurring up to 7 days after admission. Data for individual years were analysed by grouping together patients who were discharged between 1 January and 31 December inclusive.

The SMR-1 data do not refer to individual hospital admissions but are collected as 'consultant events' whereby a separate SMR-1 return is made if a patient is transferred between hospitals or even if transferred within a hospital, as would be the case with an admission to intensive care. For each episode of acute pancreatitis, it was therefore possible for any one patient to have several records in the raw data. Before analysis of incidence and mortality rate, it was necessary to merge these data such that any one episode of acute pancreatitis was represented by a single admission record. Fortunately, the records relating to each individual hospital admission were identifiable by a code number which allowed the data pertaining to any single admission to be merged using a purpose written computer program. The final data containing one record for each admission with a diagnosis of acute pancreatitis were analysed using a computer database (Microsoft Access; Microsoft Corporation, Redmond, Washington, USA).

For statistical analysis, linear trends were assessed by one-way analysis of variance. Proportional differences were compared using the χ^2 test.

Results

Over the past decade, the estimated population of Scotland has remained constant at approximately 5·14 million (data from Scottish Health Statistics 1985 and 1995). Between January 1984 and December 1995, there were 19 633 recorded discharges involving 13 727 patients from Scottish hospitals at which a diagnosis of acute pancreatitis was made. Acute pancreatitis presented in all age groups, the median age being 54 years. There were 10 898 admissions in 7083 male patients with a median age of 49 years and 8735 admissions in 6669 female patients with a median age of 62 years. The annual incidence of acute pancreatitis during this period was 318 cases per million (365 cases per million for men, 275 cases per million for women).

Patterns of incidence

The incidence of acute pancreatitis rose from 258 cases per million in 1985 to 419 cases per million in 1995. This increase followed a linear trend in both sexes. In women there was a rise from 563 to 1014 cases per year and in men from 792 to 1070 cases per year (men: $F = 140{\cdot}58$, $P < 0{\cdot}001$; women: $F = 142{\cdot}87$, $P < 0{\cdot}001$). When the incidence of acute pancreatitis in patients under the age of 40 years was compared with that in older patients, a significant increasing trend in annual incidence was observed in each group except for men under the age of 40 years (*Fig. 1*).

Pattern of deaths

The overall case mortality rate during the 12-year period was 7·5 per cent. This was higher in women (9·4 per cent) than in men (6·1 per cent) ($P < 0{\cdot}001$, χ^2 test). The case mortality rate fell steadily during the period of study from 9·1 per cent in 1984 to 6·6 per cent in 1994 despite an increase in the total number of deaths from acute pancreatitis from 120 in 1984 to 145 in 1995.

Older patients were considerably more likely to die during an attack of acute pancreatitis (*Table 1*). The case mortality rate ranged from 1 to 2 per cent in those aged less than 40 years to more than 18 per cent in those over 70 years of age. It was of interest that 58·7 per cent of all deaths occurred in patients over 70 years of age.

The proportion of in-hospital deaths occurring within the first week of admission was 53·7 per cent and ranged from as high as 61·7 per cent in 1986 to a low of 49·1 per cent in 1992. There was no evidence of an improving trend over the period of study ($F = 1{\cdot}59$, $P = 0{\cdot}236$). The proportion of deaths occurring within 3 days of admission was 40·1 per cent. The majority (78·4 per cent) of early deaths occurred in patients over the age of 60 years but the proportion of early to late deaths was similar in all age groups (*Fig 2*).

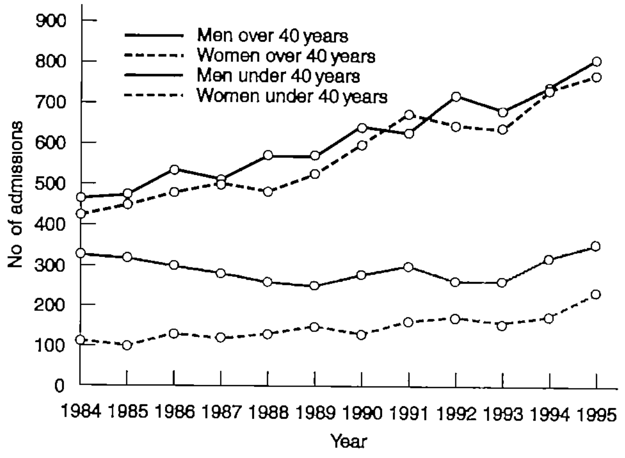

Fig. 1 Annual incidence of acute pancreatitis by age and sex

Table 1 Mortality rates from acute pancreatitis in different age groups

Age (years)	Case mortality rate (%)
<30	1·0
30–40	1·4
40–50	2·9
50–60	4·8
60–70	8·6
>70	18·8

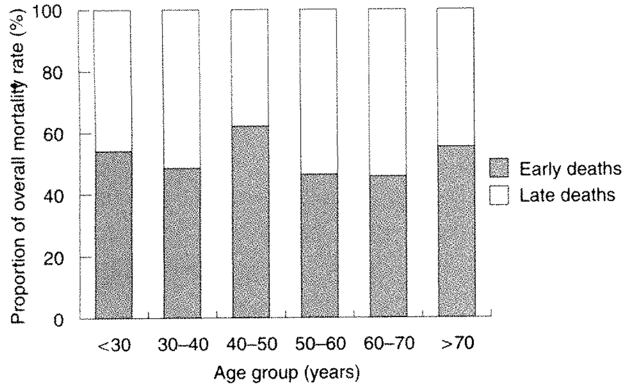

Fig. 2 Proportion of early (within 7 days of admission) to late deaths in different age groups

Discussion

This study has demonstrated a rise in the incidence of acute pancreatitis in Scotland over the past 12 years which continues a trend previously reported for the years 1961–1985[10]. The previous rise was attributed mainly to an increasing awareness of the disease as there was a dramatic fall in the case mortality rate, suggesting an increasing tendency to identify mild cases which may have previously been unrecognized. Previous studies[10,11] spanned the period of introduction of routine testing for serum amylase in patients with abdominal pain and it is therefore more likely that the trend observed in the present study represents a true increase in the incidence of the disease.

The increased incidence in young women, which was not observed in the corresponding age group in men, remains unexplained. In previous studies, the predominant cause of acute pancreatitis in this group of patients has been gallstones[11–14]. In Scotland, morbidity due to alcohol abuse has been increasing to a similar extent in both sexes over the past decade[15] and it is therefore possible that the increased incidence in young women may be a consequence of their increasing alcohol consumption.

The case mortality rate, which had fallen dramatically in the preceding decades[10], appears to have stabilized at 6–7 per cent. This is similar to that reported by recent studies[4,9,10,14] but it is likely that further improvements in outcome are possible[4]. A slight reduction in case mortality rate was observed in the present study although the actual number of deaths each year continued to increase. It is therefore difficult to ascertain whether this trend can be attributed to improvements in patient care or to an increasing incidence of mild attacks.

The association between increasing age and death from acute pancreatitis is well described[4,10,11,14] but the mortality rate of 18·8 per cent in patients over 70 years of age serves to reiterate the need for thorough supportive care in this group of patients, who often have significant co-morbidity. The association between co-morbidity and outcome in this group of patients was reported by Fan and colleagues[16]; the mortality rate associated directly with acute pancreatitis in patients aged over 70 years was similar to that in younger patients although the total hospital mortality rate was much higher. Older patients may therefore have a fatal outcome from a relatively mild attack of acute pancreatitis. The relationship between age and mortality rate helps explain some of the reported accuracy of the Acute Physiology And Chronic Health Evaluation II score and other multiple factor scoring systems in predicting outcome from acute pancreatitis[17,18]. The effect of age on mortality rate from acute pancreatitis makes the evaluation of new treatments difficult as outcome obviously relates to the cardiorespiratory reserve of patients in addition to the severity of the individual attack.

Early deaths, which are commonly associated with MODS, accounted for 40–60 per cent of in-hospital deaths in all age groups and this proportion did not improve over the past decade. The finding that the proportion of deaths occurring within 1 week of admission was not influenced by age suggests that co-morbidity alone does not account for the high early mortality rate observed in this study. The high proportion of early deaths persists despite perceived improvements in supportive care and advances in understanding of the pathophysiology of early organ failure in acute pancreatitis[19].

The proportion of early deaths in the present study was higher than that reported in recent prospective studies, but these have either adopted stringent entry criteria[7,8] or have been based around specialist centres[20]. Sick, elderly patients may be considered unsuitable for transfer to specialist units and patients with the most severe attacks may die before transfer can be arranged. Of particular relevance here is the finding that 40 per cent of all deaths occurred within 3 days of hospital admission. In the authors' experience, few patients are transferred within this time. It is therefore likely that such reports underestimate the true number of early deaths from acute pancreatitis.

The high early mortality rate in Scotland as a whole suggests that there is a need to improve the early recognition of severe pancreatitis to allow targeting of resources to these patients or their transfer to a centre with high-dependency and intensive care facilities, with a level of urgency similar to that currently employed in the management of patients with suspected myocardial infarction. Such centres require specialist imaging to be available (including endoscopic retrograde cholangiopancreatography, contrast-enhanced computed tomography and possibly magnetic resonance imaging) as well as a team with expertise in the surgical management of acute pancreatitis[21].

The accuracy of Scottish Hospitals In-Patient Statistics is obviously determined by the quality of data recorded by medical and clerical staff, although regular audit of such data is undertaken. In a study from the Grampian region of Scotland[22], it was estimated that almost half of all cases of acute pancreatitis were not recorded as such in the computer-linked diagnostic index. It is unlikely, however, that there have been significant changes in the accuracy of data recording over the past decade, an assumption which enables analysis of trends in incidence and outcome during this period.

In conclusion, there has been a steady increase in the incidence of acute pancreatitis in both sexes in Scotland during the past decade, particularly in young and middle-aged women, and there has been an associated fall in the case mortality rate. The proportion of deaths occurring during the first week of admission was 40–60 per cent and has not declined despite perceived improvements in supportive care. The mortality rate in elderly patients remains alarmingly high but the ratio of early deaths to late deaths is similar in all age groups. There remains an urgent need to improve early recognition of severe pancreatitis coupled to a willingness on behalf of clinicians to transfer these patients at an early stage to a centre in which the facilities necessary for the management of these patients are available[21].

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Evaluation of pylorus-preserving pancreatoduodenectomy with the Imanaga reconstruction by hepatobiliary and gastrointestinal dual scintigraphy

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Background: Following pylorus-preserving pancreatoduodenectomy (PPPD), most surgeons use gastrointestinal reconstruction with an end-to-side duodenojejunostomy placed distally to the pancreatojejunostomy and choledochojejunostomy. In contrast, the authors have consistently used PPPD with the Imanaga reconstruction (PPPD-Imanaga) which consists of end-to-end duodenojejunostomy, end-to-side pancreatojejunostomy and choledochojejunostomy, performed in that order. In this study, the movement of bile and food after PPPD-Imanaga was evaluated to document the functional advantages of this method.

Methods: Twenty-four patients who had undergone PPPD-Imanaga were subjected to hepatobiliary and gastrointestinal dual scintigraphy. The interval between operation and scintigraphy ranged from 28 days to 67 months. Six of the 24 patients underwent repeated dual scintigraphy for the observation of temporal changes in gastrointestinal function.

Results: The incidence of biliogastric reflux and bile stasis in the jejunal loop was markedly decreased at times later than 2 months after operation. Delay of gastric emptying and bile evacuation, sometimes accompanied by stasis in the jejunal loop, affected the mixing status of bile and food at 1 h after the beginning of imaging. A majority of the patients, however, had a satisfactory mixing status at 2 h.

Conclusion: The Imanaga reconstruction appears to be a recommendable procedure following PPPD, in light of the bile and food movement achieved in the gastrointestinal tract.

Paper accepted 27 May 1999

British Journal of Surgery 1999, 86, 1306–1311

Introduction

Pylorus-preserving pancreatoduodenectomy (PPPD) was first designed by Traverso and Longmire[1] to minimize complications related to gastric resection, such as early satiety, gastrojejunal ulceration and bile reflux gastritis, as well as diarrhoea and dumping. Various options exist for reconstructing the pancreatobiliary and digestive tracts following PPPD. Pancreatogastrostomy with an end-to-end duodenojejunostomy has recently been advocated as a complement to PPPD[2,3], but a majority of surgeons prefer a reconstructive technique which entails end-to-side duodenojejunostomy placed distally to the pancreatojejunostomy and choledochojejunostomy (PPPD with an end-to-side duodenojejunostomy is generically called PPPD-Traverso below).

The authors first performed a PPPD with gastrointestinal reconstruction which entails an end-to-end duodenojejunostomy, end-to-side pancreatojejunostomy and choledochojejunostomy, performed in that order (*Fig. 1*), in 1986. This procedure was named PPPD-Imanaga after Dr H. Imanaga, who designed a conventional pancreatoduodenectomy with gastrointestinal continuity achieved by creating an end-to-end gastrojejunostomy, followed by an end-to-side pancreatojejunostomy and, finally, a choledochojejunostomy[4]. Since then, the authors have consistently used the PPPD-Imanaga in patients with malignant and benign disorders of the pancreatic head and periampullary region[5–7].

PPPD-Imanaga, which leaves no blind intestinal segment, simulates the normal anatomical arrangement. PPPD-Imanaga therefore theoretically provides a physiological mixture of food and fresh bile in the jejunum, which is similar to that in normal subjects. However, this theoretical advantage of PPPD-Imanaga may also be affected by several other factors. To test gastrointestinal

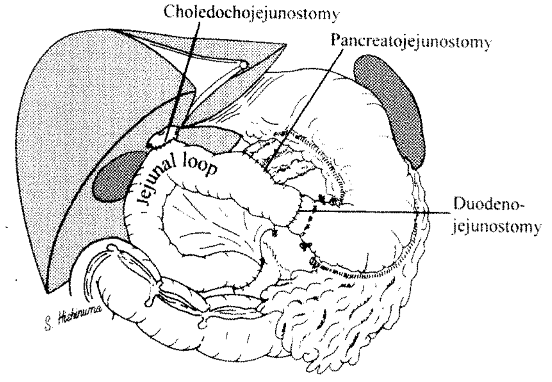

Fig. 1 Pylorus-preserving pancreatoduodenectomy with gastrointestinal reconstruction by the Imanaga method. An end-to-end duodenojejunostomy, end-to-side pancreatojejunostomy and end-to-side choledochojejunostomy were created sequentially

function after PPPD-Imanaga, the movement of fresh bile and food after PPPD-Imanaga was evaluated using hepatobiliary and gastrointestinal dual scintigraphy.

Patients and methods

Between December 1986 and December 1998, 64 patients underwent a PPPD-Imanaga at the Tochigi Cancer Centre, 24 of whom were the subjects of this study. The diagnosis was cancer of the pancreatic head in 12 patients, cancer of the periampullary region in 11 and arteriovenous malformation of the pancreatic head in one. There were ten men and 14 women, ranging in age from 37 to 85 (median 67) years. The 23 patients with malignant disease had no evidence of cancer recurrence. The interval between operation and scintigraphy varied from 28 days to 67 months (median 68 days). Six of the 24 patients underwent repeated scintigraphy for the observation of serial changes of gastrointestinal function in relation to the time after operation. Two normal subjects were also enrolled in this study.

After receiving a full explanation of the purpose and procedures of the study, the patients signed an informed consent statement. This study was approved by the ethics committee of the Tochigi Cancer Centre.

Operative procedure

As the first step in gastrointestinal reconstruction, the proximal jejunum was elevated through the transverse mesocolon. The distal end of the duodenum was first anastomosed end to end to the jejunum. Second, an end-to-side pancreatojejunostomy with a mucosa-to-mucosa anastomosis was performed 2–3 cm distal to the duodenojejunostomy. Third, an end-to-side choledochojejunostomy was created as shown in *Fig. 1*.

Hepatobiliary and gastrointestinal dual scintigraphy

After fasting overnight, each patient was given a meal of two custard puddings which contained 0·5 mCi ^{113m}In-radiolabelled diethylenetriaminepenta-acetic acid (^{113m}In-DTPA). The patient was then placed supine under a large-field-of-view digital γ camera (Starcam 400 A/CT; GE Medical Systems, Milwaukee, Wisconsin, USA) fitted with a low-energy collimator. A bolus intravenous injection of 5 mCi ^{99m}Tc-radiolabelled *N*-pyridoxyl-5-methyltryptophan (^{99m}Tc-PMT) was given immediately after the patient finished consuming the meal. The start of imaging was taken as time zero. An anterior 60-s image was acquired in a 128 × 128 matrix using double photopeaks with 20 and 10 per cent energy windows centred over 245 keV and 140 keV respectively. Dynamic scintiphotos (frames taken at 1-min intervals) of the abdomen were recorded on magnetic tape over a period of 64 min. At 2 h after the beginning of imaging, the patient was re-placed supine, and an anterior 60-s image was taken.

The 64 frames collected were then displayed in a cine mode that cyclically showed the serial images with a speed of four frames per s. By monitoring the movement of the ^{113m}In-DTPA and ^{99m}Tc-PMT images, regions of interest (ROIs) were then drawn manually for the stomach, duodenojejunostomy, choledochojejunostomy and upper portion of the jejunum (*Fig. 2*). The time–activity curve for each ROI was also computed, as shown in *Fig. 2*, and the percentage ^{113m}In-DTPA activity retained in the ROI for the stomach (percentage gastric retention) at 1 h was then calculated. The starting time of bile evacuation into the jejunal loop, subsequent bile stasis therein and biliogastric reflux were assessed by monitoring the cine mode images and time–activity curves of ^{99m}Tc-PMT scintigraphy. Next, the red-coloured ^{113m}In-DTPA image and green-coloured ^{99m}Tc-PMT image were displayed simultaneously. The mixing of these two isotopes appeared as a yellow-coloured image. By this technique, the starting time and subsequent status of mixing of bile and food were evaluated. In each patient, the mixing status at 1 and 2 h after the beginning of imaging was classified visually into three grades (good, fair and poor) according to the extent of the yellow image (*Fig. 3*).

Statistical analysis

Results are expressed as mean(s.d.). Statistical analysis was performed with Fisher's exact test or Mann–Whitney *U* test, with significance defined as $P < 0.05$.

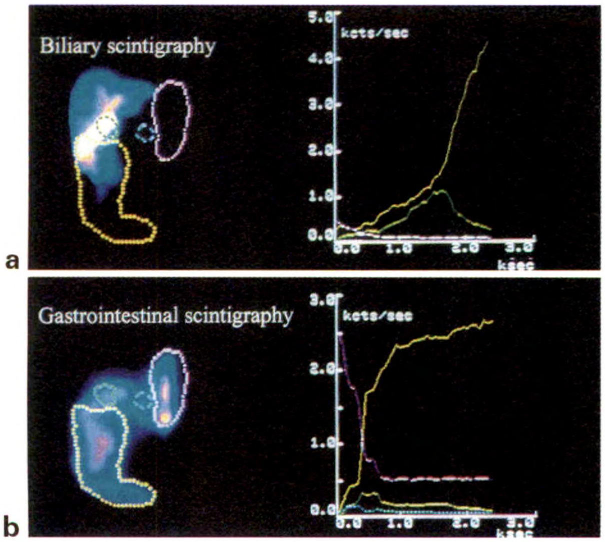

Fig. 2 Regions of interest (ROIs) and time–activity curves of dual scintigraphy. ROIs were drawn for the stomach, duodenojejunostomy, choledochojejunostomy and upper portion of the jejunum. **a** Hepatobiliary and **b** gastrointestinal scintigraphy is shown. The blue curved line in **a** cannot be identified visually because it is quite close to the baseline

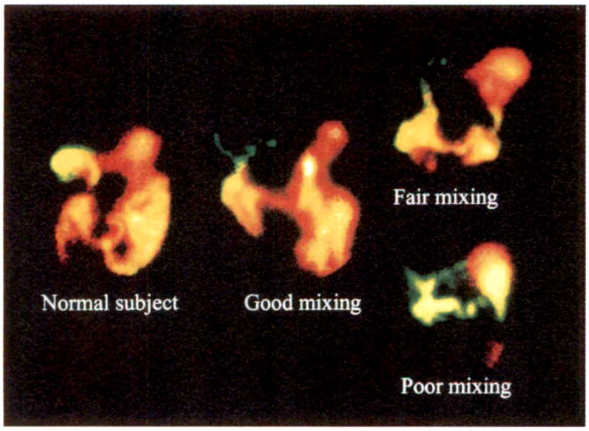

Fig. 3 Examples of poor, fair and good mixing of bile and food, classified by the extent of the yellow portion at 1 h after the beginning of imaging. Mixing status in a normal subject is also shown

Results

Normal subjects

The two normal subjects showed 43 and 66 per cent gastric retention at 1 h after the beginning of imaging. Neither bile stasis in the upper jejunum nor biliogastric reflux was observed in either subject. Bile evacuation into the duodenum started at 10 and 11 min, and mixing of bile and food started at 10 and 15 min respectively. The mixing status in one of the two normal subjects is shown in *Fig. 3*.

Mixing status at 1 h in patients (*Table 1*)

Results of the initial study for the patients who underwent repeated scintigraphy were used to compile *Table 1*. The status of mixing of bile and food at 1 h was judged to be good in nine of the 24 patients, fair in ten and poor in five. Bile stasis in the jejunal loop was observed in all mixing groups but its incidence was highest in the poor mixing group. Comparison between the good and fair mixing groups showed no significant differences in percentage gastric retention and the starting time of mixing ($P = 0.05$ and $P = 0.07$ respectively), but the starting time of bile evacuation in the fair mixing group was significantly delayed ($P = 0.03$). Compared with the good mixing group, the poor mixing group showed significant differences in percentage gastric retention and the mixing starting time ($P = 0.003$ and $P = 0.009$ respectively) as well as in the starting time of bile evacuation ($P = 0.01$).

Gastrointestinal function at different times after operation

The 24 patients were divided into two groups according to the interval between operation and scintigraphy: in group 1 ($n = 11$) scintigraphy was performed within 2 months of operation (median 41 (range 28–59) days); in group 2 ($n = 13$) scintigraphy was performed more than 2 months after operation (median 9 months (range 68 days to 67 months). Four patients in group 1 and two in group 2 underwent repeated dual scintigraphy. In these six patients, the data from the initial scans were compared with those of the patients who underwent dual scintigraphy once only.

Table 1 Characteristics of patient groups according to mixing status at 1 h

Mixing status at 1 h	No. of patients	No. with bile stasis	Gastric retention at 1 h (%)*	Starting time of bile evacuation (min)*	Starting time of mixing (min)*
Good	9	2	41·4(19·8)	13(6)	14(6)
Fair	10	3	61·7(24·0)	22(10)†	21(8)
Poor	5	3	83·6(10·4)†	22(7)†	37(17)†

*Values are mean(s.d.). †$P < 0.05$ *versus* patients with good mixing (Mann–Whitney *U* test)

Table 2 Bile movement at different times after operation

	Time after operation (months)	No. of patients	Starting time of bile evacuation (min)*	Bile stasis†		Biliogastric reflux	
				+	−	+	−
Group 1	≤2	11	16(7)	6	5	4	7
Group 2	>2	13	21(10)	2	11	0	13

*Values are mean(s.d.). †Bile stasis in a jejunal loop

Table 3 Mixing of bile and food at different times after operation

	Time after operation (months)	No. of patients	Starting time of mixing (min)*	Gastric retention at 1 h (%)*	Mixing status at 1 h			Mixing status at 2 h		
					Poor	Fair	Good	Poor	Fair	Good
Group 1	≤2	11	21(14)	62·7(18·3)	2	5	4	2	3	6
Group 2	>2	13	20(9)	55·2(30·2)	3	5	5	2	2	9

*Values are mean(s.d.)

Bile movement (Table 2)

There was no difference in the starting time of bile evacuation between groups 1 and 2 ($P = 0{\cdot}32$). Six of the 11 patients in group 1 and two of 13 in group 2 had bile stasis in the jejunal loop ($P = 0{\cdot}08$). Four of the 11 patients in group 1 but none in group 2 showed biliogastric reflux ($P = 0{\cdot}03$). Three of the four patients with biliogastric reflux in group 1 also had bile stasis in the elevated jejunal loop.

Mixing of bile and food (Table 3)

The starting time of mixing was similar in the two groups ($P > 0{\cdot}99$). The percentage gastric retention was also similar ($P = 0{\cdot}68$). A majority of the patients showed fair or good mixing in the jejunum, and the mixing status was found to be better at 2 h than at 1 h, especially in group 2. Two of 11 patients in group 1 and two of 13 in group 2 showed poor mixing even at 2 h.

Temporal changes in gastrointestinal function in individual patients

Three of the four patients in group 1 showed better results in the second study, which was performed more than 2 months after operation. Bile stasis in the jejunal loop, which the initial study had revealed in these three patients, had disappeared by the time of the second study. The high percentage gastric retention observed at the initial study was decreased in the second study, resulting in better mixing status. In the remaining patient, however, poor mixing at 2 months remained unchanged even at 13 months. One patient in group 2 showed similar results in the first and second studies. In the second patient in group 2 the mixing status at 1 h was improved in the later study. None of the six patients demonstrated biliogastric reflux at any time after operation.

Discussion

PPPD has been demonstrated to be associated with a normal gastrointestinal hormonal milieu and a better weight gain after operation than conventional pancreatoduodenectomy[8–11], and has become a common procedure for disorders of the pancreatic head and periampullary region. A majority of surgeons prefer PPPD-Traverso, but the authors have used PPPD-Imanaga, which restores the alimentary tract without a blind intestinal segment so that food, pancreatic juice and bile can mix physiologically in the upper portion of the jejunum. Furthermore, it has been demonstrated previously that PPPD-Imanaga can be performed with acceptable morbidity and mortality rates[7]. The nutritional advantage of PPPD-Imanaga over PPPD-Traverso has been shown by Ogata *et al.*[6]. They reported that patients who underwent PPPD-Imanaga or PPPD-Traverso regained a mean of 90 per cent of preoperative weight 6 months after operation, but the weight gain at 18 months after PPPD-Imanaga was better than that after PPPD-Traverso. In the present study, the movement of bile and food in the gastrointestinal tract after PPPD-Imanaga was examined in order to document the functional advantages of PPPD-Imanaga.

Many investigators have reported that delayed gastric emptying in the early postoperative period is one of the leading causes of morbidity following PPPD. In long-term follow-up studies, however, several investigators have confirmed that a majority of patients regain normal gastric emptying after PPPD[10,12–16]. Braasch *et al.*[10] used isotopes to measure the gastric emptying of liquid and solid food, and found no significant differences between five control subjects and five patients who had undergone PPPD. Traverso and Longmire[15] reported that all eight patients studied 2–12 months after PPPD showed normal gastric emptying during a barium meal. Kobayashi *et al.*[17] suggested that liquid-phase gastric emptying recovers within 2–5 weeks and solid-phase emptying recovers approximately 3 months after PPPD. On the other hand, Williamson *et al.*[18] reported that isotopic test results of gastric emptying were frequently abnormal between 2 months and 5 years after PPPD, but that symptoms were uncommon. The present study also showed that percentage gastric retention at 1 h, which is an indicator of gastric emptying, was not significantly different within and later than 2 months after operation, and that certain patients still had high percentage gastric retention even after 2 months. Repeated scintigraphy in individual patients, however, showed that the high percentage gastric retention within 2 months of operation decreased to a lower level at more than 2 months after the procedure, suggesting that gastric emptying improves along with the recovery of pyloric function with time.

The recovery of pyloric function after PPPD-Imanaga was also evidenced by the absence of biliogastric reflux in patients who were examined more than 2 months after operation. Several authors have documented biliogastric reflux in the late postoperative period after PPPD-Traverso or PPPD with Roux-en-Y reconstruction[10,14,18,19]. In these series, biliogastric reflux was observed in approximately half of the patients. It is noteworthy that none of the 13 patients who were examined more than 2 months after PPPD-Imanaga showed biliogastric reflux, although two had bile stasis in the jejunal loop. It is reasonable therefore to claim that PPPD-Imanaga will minimize the risk of reflux bile gastritis at times later than 2 months after operation.

Those investigators who emphasized good recovery of gastric emptying after PPPD-Traverso did not refer to the status of bile and food mixing[10,12–16]. In the present study, the patients with good mixing at 1 h showed patterns of bile and food movement very similar to those of normal subjects. Fewer than half of the 24 patients, however, showed good mixing at 1 h, which suggests that good mixing at 1 h cannot be achieved by the physiological arrangement of gastro-intestinal continuity alone. The authors estimate that one-third to one-half of the gastric contents should be emptied during the first hour in order to obtain good mixing of fresh bile and food at 1 h. Good mixing at 1 h also requires sufficient motility of the jejunal loop, which prevents stasis. Moreover, appropriate timing of bile evacuation into the jejunal loop is required. Unless these requirements are fulfilled, it is difficult to obtain good mixing at 1 h. The mixing status at 2 h, however, was found to be better than that at 1 h, and two-thirds of the patients showed good mixing at 2 h. Poor mixing at 2 h was found in only four of the 24 patients.

The magnitude of operation for pancreatic head and periampullary cancer has often caused poor postoperative nutritional status. To improve such poor nutritional status, reconstructive techniques must be devised for obtaining better gastrointestinal function. With few exceptions, gastrointestinal function after PPPD-Imanaga is well recovered at times later than 2 months after operation, and this reconstruction provides reasonably satisfactory mixing of fresh bile and food if there is no gastric retention. PPPD-Imanaga can therefore be recommended for patients with disorders of the pancreatic head and periampullary region.

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Original article

Endoscopic totally extraperitoneal repair of bilateral inguinal hernias

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Background: Recurrence rates associated with bilateral inguinal hernia repair with a giant prosthesis (Stoppa procedure) are low. Endoscopic totally extraperitoneal bilateral inguinal hernia repair with a giant prosthesis combines the low recurrence rate of the Stoppa repair and the advantages of minimally invasive surgery. The aim of this retrospective study was to investigate whether extraperitoneal bilateral inguinal hernia repair could be performed by the minimally invasive, totally extraperitoneal approach.
Methods: From February 1993 to January 1998, 98 patients with bilateral inguinal hernias underwent surgery. A polypropylene 30 × 10 cm rectangular mesh or a 30 × 10/15 cm 'slipmesh' was used. Follow-up, including a physical examination, of 96 per cent of patients was performed.
Results: Median operative time was 60 min. Mostly minor intraoperative complications occurred. Conversion was required for two patients. Apart from one patient with a necrotic fasciitis who died from respiratory failure, only minor postoperative complications (10 per cent) occurred. Median hospital stay was 1 (range 1–21) days. Median recuperation time was 5 (range 1–22) days. Median follow-up (96 per cent) was 32 (range 7–57) months; there were six recurrences among 34 hernias in the group of 17 patients treated with 10 × 30 cm mesh and two (1 per cent) in the group that received 30 × 10/15 cm mesh (162 hernias in 81 patients).
Conclusion: The endoscopic approach for the Stoppa procedure for bilateral inguinal hernia repair is a reliable method with minor complications. It ensures a short recuperation time and the recurrence rate is low owing to adequate overlap of the hernial defect when a 'slipmesh' is used.

Paper accepted 26 May 1999

British Journal of Surgery 1999, 86, 1312–1316

Introduction

Some studies have reported an increased morbidity rate following bilateral inguinal hernia repair compared with unilateral hernia repair[1,2]; other authors disagree that the morbidity rate for bilateral inguinal hernia repair is higher when a tension-free repair is performed[3–5]. In view of the disadvantages of sequential unilateral hernia repair, such as higher total expenses and more sick leave, simultaneous repair is to be preferred[1,4–7]. From the standpoint of morbidity, an endoscopic technique for bilateral inguinal hernia repair is attractive since it is known to cause less postoperative pain and ensures more rapid recovery than conventional hernia repair[1,2,8–10]. Furthermore, the recurrence rate for conventional hernia repair without a mesh prosthesis remains high[11]. The prosthetic repair of bilateral inguinal hernias by the preperitoneal approach, as described by Stoppa and Warlaumont, has reduced recurrence rates significantly[1,12,13].

Endoscopic totally extraperitoneal bilateral inguinal hernia repair with a giant prosthesis combines the low recurrence rate of the Stoppa prosthetic repair of groin hernias and the advantages of minimal invasive surgery[4,14–16].

Patients and methods

Ninety-eight patients with bilateral inguinal hernias at physical examination, who were fit for general anaesthesia and did not have an infection of the abdominal wall, underwent surgery. Peroperative hernia classification was performed as proposed by Nyhus[12]. All operations were performed by three staff surgeons experienced in endoscopic surgery. The procedure used was standardized for all cases. The essential steps of total extraperitoneal repair have been described by Liem *et al.*[17].

For the first 17 cases of this study a 10 × 30 cm polypropylene prosthesis (Prolene; Ethicon, Edinburgh, UK) was used. However, a relatively large number of medial recurrences apparently occurred owing to insufficient overlap of the medial orifice when using the 10 × 30 cm prosthesis; therefore a 10/15 × 30 cm 'slipmesh' polypropylene prosthesis was used for the subsequent 81 patients. The 'slipmesh' (*Fig. 1*) is a tailored mesh of 15 × 30 cm. The 'slip' can be pulled into a position which results in better coverage of the area of the direct hernias.

When intraoperative complications led to the need for conversion to another endoscopic or an open technique, the procedure was chosen by the operating surgeon.

After operation patients were mobilized directly and were allowed to leave the hospital as soon as they felt able as long as postoperative complications requiring clinical care had not occurred.

The first 54 patients were seen at regular 3-month intervals during the first year after operation and then annually by the authors. The other patients (43) were seen 1 week after operation and, if no problems occurred, further follow-up was done on demand. For the present study initial data and data recorded during follow-up were collected from patient records. Operative time was defined as the time from the first incision to the last suture. Intraoperative complications (diffuse haemorrhage or bleeding from an epigastric vessel, peritoneal defects), postoperative complications (large haematomas of the abdominal wall, seroma, paraesthesia, wound infection, urine retention, mesh infection, pneumopericardium) and conversion of the totally extraperitoneal operation to an endoscopic transabdominal or open procedure were noted. Length of hospital stay (number of days in hospital after operation), recuperation time (number of days needed for recovery before returning to work or full daily activities) and recurrence of a hernia were assessed. To complete this study with up-to-date recurrence rates, all patients were approached by mail or telephone and asked to report to the outpatient department for a physical examination. Appointments were made at two fixed dates at which patients (96 per cent) had a thorough physical examination performed by a staff surgeon and a senior resident (both authors of this manuscript). At this final check-up, initial data missing from patient records were collected and recurrence of the hernia was evaluated by means of a thorough physical examination.

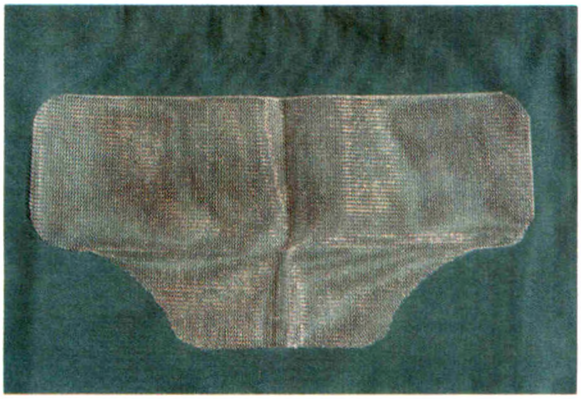

Fig. 1 'Slipmesh' prosthesis (10/15 × 30 cm)

Results

From February 1993 to January 1998, 98 patients (96 men and two women) were operated on. Their age at surgery ranged from 27 to 86 (median 60) years. Hernia localization, classified according to Nyhus, is given in *Table 1*. In 75 patients a primary bilateral inguinal hernia was diagnosed. In 14 patients the hernia was primary on one side and recurrent on the other, and in another nine patients the hernia was recurrent on both sides. The recurrent hernias had all developed after previous conventional hernia repair without the use of prosthetic material. For dissection a peritoneal dissection balloon was used in 80 cases, leading to peritoneal tears during dissection in 14 (18 per cent). In the other 18 patients dissection was performed with the endoscope leading to peritoneal tears in all instances. The median operative time was 60 (range 20–120) min.

Intraoperative and postoperative complications are summarized in *Table 2*. In one patient the epigastric vessels were injured such that clips were needed to stop the bleeding. In 30 of 32 patients with minor peritoneal tears the peritoneal defect was closed with a Polydioxanone-S (Ethicon) running suture or endoloop. Twice this was not possible: in one patient dissection difficulties owing to leakage of gas to the abdominal cavity made it necessary to convert the procedure to a transabdominal preperitoneal (TAPP) repair with a 10 × 15 cm prosthesis on each side; in the other patient the procedure was continued using the open Stoppa approach.

Postoperative complications occurred in 10 per cent of the patients, most of which were minor. Small haematomas which resolved spontaneously accounted for another 11 per

Table 1 Classification according to Nyhus of 98 patients with a bilateral inguinal hernia

Nyhus classification					
II, II	20	IIIA, IIIA	19	IIIB, IIIB	9
II, IIIA	11	IIIA, IIIB	10	IIIB, IV	3
II, IIIB	6	IIIA, IV	8	IV, IV	9
II, IV	3				

NII, Indirect hernia; NIIIA, direct hernia; NIIIB, combined hernia; NIV, recurrent hernia

Table 2 Complications among 98 patients who underwent endoscopic totally extraperitoneal repair of a bilateral inguinal hernia

	No. of patients
Peroperative complications	
Peritoneal tears	32 (33)
Conversion	2 (2)
TAPP repair	1 (1)
Open Stoppa	1 (1)
Epigastric vessel laceration	1 (1)
Postoperative complications	
Haematoma	11 (11)
Mesh infection	2 (2)
Urine retention*	2 (2)
Pneumopericardium	1 (1)
Seroma	1 (1)
Cystitis	2 (2)
Temperature (of unknown origin)	1 (1)
Paraesthesia	2 (2)

Values in parentheses are percentage. *This occurred in a patient with a pre-existing urethral stricture. TAPP, transabdominal preperitoneal

cent of 'postoperative complications'. Mild paraesthesia of the medial thigh in two patients was probably due to injury of the ilioinguinal nerve; at 3 months it had completely disappeared in both patients. The seroma needed fine-needle aspiration and the cystitis was treated with antibiotics. One mesh infection was treated successfully by ultrasonographically guided drainage and the administration of intravenous antibiotics; at follow-up no signs of ongoing infection were present. The other patient with a mesh infection suffered a dramatic necrotizing fasciitis which, although cured by extensive abdominal resection, led to his death from acute respiratory distress syndrome (ARDS) and pulmonary insufficiency.

Median hospital stay was 1 (mean 2, range 1–21) day. The patient with the infected mesh that was treated successfully and a patient who underwent dilatation of a urethral stricture were hospitalized for 14 and 21 days respectively. The patient who died from ARDS due to necrotizing fasciitis was in hospital for 21 days. The 30-day hospital mortality rate was thus 1 per cent. One patient with a raised temperature of unknown origin was hospitalized for analysis for 2 weeks until the temperature resolved spontaneously. Patients returned to work or full daily activities after a median period of 5 (mean 7, range 1–22) days.

Ninety-four of 98 patients responded to the postal questionnaire and, in some cases, subsequent telephone request; therefore follow-up with a physical examination was accomplished in 96 per cent. Median follow-up was 32 (mean 30, range 7–57) months.

Eight recurrences were diagnosed in seven patients. In six patients a unilateral recurrent inguinal hernia was seen at physical examination. In one patient a bilateral recurrent hernia was diagnosed. Five patients had noticed bulging; the other two patients were asymptomatic. Six of these recurrences occurred within the first year of surgery for a primary inguinal hernia. Six of the patients with a recurrence belonged to the group of 17 patients (34 hernias; recurrence rate 18 per cent) who received the 10 × 30 cm rectangular prosthesis. Of the 81 patients (162 hernias) with a 10/15 × 30 cm slip prosthesis, two (1 per cent) suffered a recurrence. Reintervention was performed in five cases (six hernias) by means of a TAPP procedure. This reintervention allowed the cause of the recurrence to be investigated. In all cases the recurrent hernia was located medially, and thus was probably due to insufficient overlap of the defect by the rectangular mesh or inadequate positioning of the 'slipmesh'. The two fully asymptomatic patients preferred to postpone the operation until complaints developed.

Discussion

Both the use of a prosthetic mesh to create a tension-free repair and the endoscopic technique have gained popularity in inguinal hernia surgery[3,4,9]. Stoppa and others have used the preperitoneal subumbilical approach to the retrofascial space since 1969. Advantages of this approach were the ease of separation of the retrofascial cellular space, direct access to the posterior inguinal structures, clear understanding of hernial lesions, and clear exposure of the musculopectineal opening. Furthermore, in their opinion, the retrofascial space is a natural site for prostheses to reinforce the transversalis fascia.

Although several promising reports on endoscopic inguinal hernia repair have been published[2,8,18,19], reports on endoscopic bilateral inguinal hernia repair are scarce[4,10]. As a rule these bilateral procedures are small in number and are described as part of a study on endoscopic unilateral inguinal hernia repair[8,12,18,20]. The technique most often used for these bilateral hernias is the TAPP technique with two meshes of 10 × 15 cm or one single large mesh[7]. The totally extraperitoneal procedure, however, is the preferred technique in most situations, as it is less difficult to position a large mesh[18,21,22].

The choice of a single large prosthesis might reduce the problem of mesh migration and the risk of insufficient overlap of the medial defect[10,14,21]. It is important to cover the areas of both indirect and direct (potential) hernias of the inguinal floor in all cases to reduce hernia recurrence[21]. In this study of bilateral inguinal hernia repair the Stoppa procedure was adopted in combination with an endoscopic approach. Stoppa and Warlaumont[13] reported a recurrence rate of 1·4 per cent using their technique. In their opinion the recurrences that did occur resulted from insufficient mesh size or shape since the recurrences passed through insufficient fascia under the lower edge. The same problem was encountered using the rectangular mesh in the present study and therefore a switch was made to the 'slipmesh' prosthesis which resulted in a lower recurrence rate (1 per cent).

In the present study of totally extraperitoneal repair of bilateral inguinal hernias the occurrence of intraoperative and postoperative complications was comparable to that of other reports on endoscopic inguinal hernia repair[8,9,18,21,22]. Nevertheless, two serious complications did occur. Although one of these patients did not suffer any late problems from mesh infection, the second patient died from respiratory failure during treatment of necrotizing fasciitis in the intensive care unit. For this reason selective indications for repair with prostheses (no abdominal wall infections, no other active infections), irrespective of the procedure, and careful attention to the prevention of septic complications of both conventional and endoscopic repairs are essential[13]. Antibiotics were not administered in these patients; these mesh infections were considered to be a coincidence in this subgroup of patients as mesh infections have not occurred at all in the (more than 1000) other hernia repairs performed by the authors. Operative time was comparable to, or even shorter than, that for conventional surgery.

The short hospital stay and rapid recuperation in this group are comparable to those of earlier reports[2,4,14]. Simultaneous repair of bilateral hernias which, according to some authors, is controversial in the event of open inguinal hernia repair, does not lead to extra hospitalization or longer recuperation when the endoscopic approach is applied[4,14,16]. The wide range in the length of hospital stay and the recuperation time may be explained by the extended clinical treatment of a mesh infection in one patient, the surgical treatment of an urethral stricture in another and the conversion to an open repair in two patients.

Many recurrences are not noticed by the patient and will therefore not be reported in questionnaires or during telephone interviews[4,9,11,16]. The recurrence rate was high (18 per cent) for the 17 patients (34 hernias) in whom a rectangular mesh was used. In four of these six patients reintervention took place. All of these recurrences were found to be medial. Probably the rectangular shape of this prosthesis does not give adequate coverage of the medial defects. With use of the 'slipmesh', which ensures more complete overlap of medial defects, the recurrence rate dropped to 1 per cent[14]. Recurrence in this case is most probably still due to inadequate dissection or inadequate positioning of the mesh: the prosthesis was not found in the right position medially at reintervention for the recurrent hernia. Adequate dissection and mesh positioning when using an appropriate mesh size should further decrease recurrence rates.

The results of this procedure as shown are promising. It should, however, be emphasized that a relatively long learning curve[17] is to be expected since both the introduction and the positioning of the mesh prosthesis are quite difficult.

Although this procedure is feasible the question remains as to whether it is also reasonable. Increased costs of the procedure are often mentioned as a negative feature. The decreased costs due to shorter sick leave and fewer readmissions for hernia recurrences may compensate for the higher costs of the endoscopic procedure.

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Original article

A 14-year experience with 6 cm as a criterion for surgical treatment of abdominal aortic aneurysm

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Background: It remains unclear when to recommend operation for an asymptomatic abdominal aortic aneurysm (AAA). This study examined a prospective series of patients for whom standard criteria were applied.

Methods: Some 584 consecutive patients with an AAA of diameter 3 cm or greater detected by ultrasonographic screening have been observed for up to 14 years. Repeat ultrasonographic examinations have been performed at intervals. Surgery was not considered unless the aneurysm measured 6 cm in diameter, expanded at a rate equivalent to at least 1 cm per year, caused the patient symptoms, or an iliac aneurysm was present that required treatment.

Results: Operation was performed on 127 patients; the majority (80; 63 per cent) had an aneurysm that reached 6 cm in diameter. Use of the above criteria prevented rupture in all but 24 (4 per cent) of the 584 patients over the 14-year interval. Of these 24 patients, 11 were unfit for planned surgery and eight declined operation or follow-up. Rupture in the five remaining patients (1 per cent) who were available for treatment compared favourably with the reported 30-day mortality rate for elective surgical treatment of 1·4–12 per cent.

Conclusion: Repeated observation is preferable to surgical intervention until an aortic aneurysm measures 6 cm in diameter, expands by 1 cm per annum or causes symptoms.

Presented as a poster to the 52nd Annual Meeting of the Society for Vascular Surgery, San Diego, California, USA, June 1998

Paper accepted 25 May 1999

British Journal of Surgery 1999, 86, 1317–1321

Introduction

The near 100 per cent mortality rate from a ruptured abdominal aortic aneurysm (AAA) without surgical treatment coloured early assessment of the management of asymptomatic AAA and led to recommendations for elective treatment in patients with a maximum aortic diameter as small as 3–4 cm. The indications for surgical intervention were reassessed in studies in which AAAs were detected clinically or by chance. These patients inevitably had larger aneurysms owing to the method of detection. The results of these studies led to widely applied recommendations to operate on patients with asymptomatic AAAs between 4 and 5 cm in diameter[1–4]. In contrast, post-mortem reports and observation in patients unfit for operation have suggested that rupture of an AAA less than 6 cm in diameter is relatively uncommon[5,6].

Since 1984 the Scott Research Unit has identified patients with AAA from a community-based screening programme. At the start of the programme, criteria for surgical intervention were chosen and applied prospectively. The criteria for elective surgery were: diameter of 6 cm or greater, rapid expansion, development of symptoms attributable to the AAA, or the presence of a large iliac aneurysm. The present study reports the results of this programme over 14 years.

Patients and methods

The screening programme identified 584 patients with AAA who were observed prospectively[7]. The local ethics committee granted approval for the study. Men and women, aged 65–80 years, were identified from a family doctor register. Those who accepted the invitation were scanned in a local hospital or health centre. An ultrasonographer scanned patients with the assistance of a research nurse who obtained other data and answered queries.

The maximum diameter of the aorta was measured using a linear ultrasonographic scanner. Measurements were made of the maximum anteroposterior and transverse diameters. An abnormal aorta was defined as 3 cm or more in diameter in either the anteroposterior or transverse plane.

After consultation with the family doctor, patients with an enlarged aorta were offered further scanning at an interval of 1 year if the aortic diameter measured 3–4·4 cm, or 3 monthly if the aorta measured 4·5–5·9 cm. Patients with an AAA of 4·5 cm or greater were offered an appointment at a vascular outpatient clinic on at least one occasion, when a repeat scan was performed and the result compared with previous scans. Patients' general medical fitness was also assessed.

Elective AAA surgery was considered if one or more of the following criteria were met: (1) the aorta measured 6 cm or more in diameter; (2) successive scans showed an expansion rate equivalent to more than 1 cm per year; (3) symptoms attributable to the aneurysm developed; (4) an iliac aneurysm greater than 3 cm in diameter was present. If the criteria were confirmed, the patient was assessed for suitability for AAA surgery. Patients were returned to the screening unit for continuing ultrasonographic surveillance if the criteria for operation were not confirmed. Any person who declined or who was unfit for elective operation was also offered continuing surveillance.

The outcome in terms of AAA treatment and cause of death was monitored as outlined previously[8].

Results

Invitations for screening were sent to 21 188 people, and 14 129 attended (attendance rate 67 per cent, ranging from 54 per cent at the start of the project to 75 per cent currently). An AAA (3 cm or greater) was detected in 584 patients. The overall prevalence was 6 per cent in men and 1 per cent in women. *Table 1* shows the prevalence within the various age and trial groups. The distribution of aortic diameter is shown in *Table 2*.

Some 492 patients attended at least one (median 4, range 1–28) follow-up clinic. Median duration of follow-up was 85 (range 1–167) months. Of the 584 patients with AAA detected, 260 reached at least one criterion and were considered for operation (*Table 3*). Some 111 patients underwent elective surgery (one patient died, giving a 30-day operative mortality rate of 1 per cent). In addition, nine patients underwent emergency operation for rupture (four died by 30 days after operation), six had urgent operation for acute symptoms (one died by 30 days), and one patient had AAA surgery for a false aneurysm. The overall mortality rate in the 127 patients who underwent operation was 5 per cent (six patients).

A total of 145 AAAs expanded by more than 1 cm per annum. Only 28 per cent (40 of the 145) of patients went on to have elective surgical treatment. The remaining 105 patients underwent continuing surveillance by the screening team. Only two (1 per cent) of the 260 patients who reached the criteria developed symptoms alone, but both had surgery. Two patients underwent operation because of iliac artery involvement.

Three patients were identified who had AAA repair before reaching the criteria for considering elective operation. One patient, who was taking warfarin, had rupture of an AAA that had measured 4·2 cm 4 months earlier. One patient with a 3·7-cm AAA moved from the area and had AAA surgery 1 year later. One patient had only recently been recruited by the screening programme, but had previously been under surveillance by the vascular team and the aneurysm was assessed as expanding rapidly.

During follow-up of up to 14 years, 217 patients have died. Information on cause of death was obtained from the

Table 1 Prevalence of abdominal aortic aneurysm by age group and sex

		Scanned group									
		Men			Women			Total			
Age group (years)	No. invited for screening	No. scanned	AAA	Prevalence (%)	No. scanned	AAA	Prevalence (%)	No. scanned	AAA	Prevalence (%)	Attendance (%)
65–80*	11 941	3346	263	8	4226	59	1	7 572	322	4	63
65†	6 667	3363	143	4	1363	7	1	4 726	150	3	71
70†	1 964	1335	85	6	138	0	0	1 473	85	6	75
75†	616	358	27	8	–	–	–	358	27	8	58
Total	21 188	8402	518	6	5727	66	1	14 129	584	4	67

*Randomized study of patients aged 65–80 years recruited from nine general practices; †continuing study involving patients recruited in their 65th, 70th and 75th year from 24 general practices local registrars of deaths' returns to the Local Health Authority. Post-mortem reports were obtained where possible. Of those who died, 77 per cent (168 of 217) died from causes other than ruptured AAA, with the aneurysm intact and not having had AAA surgery. Twenty-eight died at some time after AAA surgery from causes other than ruptured AAA. Twenty-one died from ruptured AAA, seven of whom underwent emergency operation.

In all, aneurysm rupture occurred in 24 patients (4 per cent; including the 21 mentioned above) of the 584 who were detected with AAA. Nine had emergency surgery, and five survived. All lived for at least 1 year and three are still alive. Of the 24 patients who had a ruptured AAA, 11 were unfit for planned surgical intervention, six declined surgery or follow-up and three were booked for operation or an outpatient appointment but had rupture of the AAA before treatment. The 11 patients were deemed unfit because of severe infirmity (*Table 4*). In addition, two patients subsequently declined further follow-up. Four aneurysms ruptured before reaching the criteria for considering operation; two of these patients had declined further follow-up. The 19 patients who declined or were unfit for elective surgery would not have been available for treatment, whatever the criteria for AAA surgery. Only five (1 per cent) of 584 patients with ruptured AAA would have been available for treatment.

Clinical workload in aneurysm screening is affected by the aortic diameter selected for consideration of operation, as well as the patient age bands and sex chosen for screening. At the time of the initial scan, 18 per cent of men and 44 per cent of women with an AAA were aged between 75 and 80 years. Seven per cent of all patients with aortic aneurysm had an aorta that measured over 6 cm, 16 per cent measured over 5 cm, and 35 per cent measured over 4 cm. During follow-up of the 584 patients with AAA (median 85 months), 111 aneurysms (19 per cent) had aortic diameters that reached 6 cm (i.e. 6 cm at initial scan or on follow-up). In 204 patients (35 per cent) the aneurysm diameter had reached 5 cm and in 343 (59 per cent) it had reached 4 cm at the initial scan or during observation[9].

Table 2 Distribution of abdominal aortic aneurysm size at initial detection

	Initial AAA size (cm)				
	3–3·9	4–4·9	5–5·9	6+	Total
Men	329	106	42	41	518
Women	51	7	6	2	66
Total	380 (65)	113 (19)	48 (8)	43 (7)	584

Table 4 Details of 11 patients with abdominal aortic aneurysm rupture unfit for elective treatment

Patient no.	Sex	Age (years)	Clinical details
1	M	84	Myocardial infarction, angina
2	F	74	Angina, transient ischaemic attack, dyspnoea
3	M	83	Disabling stroke
4	M	86	Dementia
5	M	82	Gross respiratory disease, obese
6	M	76	Dyspnoea (declined further follow-up)
7	M	79	Left ventricular failure, infirmity
8	M	84	Myocardial infarct, angina
9	M	80	Myocardial infarction, gross respiratory limitation
10	F	80	General infirmity (declined further follow-up)
11	M	74	Severe cardiac problems following aortic valve repair

Table 3 Patients reaching criteria for considering abdominal aortic aneurysm surgery and having an operation

			Criteria			
	No. of patients	No. reaching criteria	Diameter ⩾ 6 cm	Expansion rate > 1 cm per year*	Iliac aneurysm > 3 cm	Symptoms alone
No. with AAA	584	260	111 (43 initial, 68 reached)	145	2	2
No. going on to surgery	127 (22)	124 (48)	80 (72) (34 (79) initial, 46 (68) reached)	40 (28)	2	2

Values in parentheses are percentages. *Less than 6 cm in diameter. AAA, abdominal aortic aneurysm

Discussion

The diameter at which operation is indicated for asymptomatic AAA has been a source of debate because, until recently, there has been a lack of knowledge of the natural history of the disease[10]. AAAs of less than 5 cm in diameter occasionally rupture[11] and there have been recommendations that operation should be considered in patients with an AAA 4 cm or greater in diameter[2].

In 1984, when the Chichester aneurysm screening programme started, Bernstein and Chan[12] had reported the results of a study of poor-risk patients with an AAA greater than 6 cm in diameter. With repeated ultrasonography and the application of specific criteria to define which patients should have elective surgery, the rupture rate was less than 5 per cent. As there was no information at that time on the indications for operation in an unselected population with AAA identified by screening, criteria similar to those of Bernstein and Chan were adopted in Chichester.

Ultrasonographic screening can visualize the aorta in 97 per cent of those imaged[7]. The trial population was not preselected on any grounds other than age, unlike previous reported studies[13–15]. The population followed was therefore representative of the entire AAA population within the age group screened, and not selected by clinical presentation.

Most of the patients (77 per cent) with an aneurysm who died did so from another cause with the aneurysm intact. This observation is similar to post-mortem findings where 75 per cent of patients with AAA died from problems unrelated to the aneurysm[5]. AAA surgery in these patients would not have increased their longevity. Nearly half (45 per cent) of the patients with aortic aneurysm reached at least one of the criteria for considering surgery over the 14-year observation, but only 127 (22 per cent) went on to have an operation. Of those initially below 6 cm (541 patients), 90 (17 per cent) underwent operation. This contrasts with the findings of the UK Small Aneurysm Trial, which found that 61 per cent of patients initially allocated to surveillance had an operation (321 of the 527 with AAA initially 5·5 cm or less)[16]. This difference is likely to be a reflection of the small proportion of screen-detected AAAs and the large number of centres involved in this trial, rather than a difference in the potential rupture rate.

Whilst the criterion of an expansion rate of 1 cm per year or its equivalent (3 mm over a 3-month period) identified a large proportion of patients who needed to be assessed for operation (25 per cent (145 of 584) of all AAAs detected), only 40 required treatment. This criterion was chosen at the outset to be cautious and not to overlook any patients who were at risk of rupture. At that time there was an absence of good information on the risk of rupture in patients with an AAA between 4 and 6 cm. These expansion criteria have proved to be oversensitive, as recent research[17–19] has indicated that the ultrasonographic error in measurement is ± 0·5 cm. The criterion now recommended is a 1-cm expansion in 1 year and not the equivalent expansion over 3 months. The recent report on AAA growth rates from Chichester supports this view and has confirmed the low risk of rupture in small AAAs, particularly in those with an expansion rate of less than 0·5 cm per year[20].

Observation of the 584 patients avoided aneurysm rupture in all but 24 patients (4 per cent). Of these, 19 were either unfit for, or declined, planned surgery or declined follow-up. This group would not have been available for treatment whatever AAA diameter had been used. The remaining five patients with AAA rupture (1 per cent of all AAAs detected) would have been available for planned treatment. This gives a mortality rate from rupture of 1 per cent in those available for treatment. Observation to 6 cm therefore carried a small risk of rupture using the present criteria, but the risk was lower than the reported mortality rate following active intervention.

Elective AAA repair carries an operative mortality rate reported as between 1·4 and 12 per cent[21–23]. Active intervention in the present study of patients with an aortic diameter of 5 cm would have doubled, and at 4 cm tripled, the surgical workload, with concomitant deaths related to the increased number of operations. Not only might early intervention increase the mortality rate, but it also involves unnecessary surgery on more than three-quarters of patients who subsequently die from other causes with the aneurysm intact.

The frequency of observation (yearly for aneurysms of 3·0–4·5 cm and 3 monthly for those of 4·6–5·9 cm) is effective in identifying the majority of patients at risk of rupture, although screening at longer intervals may be adequate[24].

The Small Aneurysm Trial confirmed that surveillance of asymptomatic AAAs measuring under 5 cm in diameter is safe and that operation does not provide a long-term survival advantage[16]. Although there has been criticism that 20 per cent of the cases were operated on for tenderness[25], much of the comment on this trial supports the conclusion of the present study[9,26]. Observation of patients until the aneurysm reaches 6 cm or displays rapid expansion or symptoms is preferable to early surgical intervention. The Multi-centre Aneurysm Screening Study will give additional information when it reports in the year 2003.

The results of practice over 14 years in Chichester, combined with the report of the Small Aneurysm Trial[16], provide clinicians with evidence that operating on small asymptomatic AAAs is not in patients' best interests, as long as surveillance at regular intervals is undertaken to detect rapid expansion.

Acknowledgements

The authors are grateful for financial support from the Cardiovascular Disease and Stroke Programme, Research and Development Division, NHS Executive, and for continuing commitment by the Chichester screening team to the project.

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External anal sphincter atrophy on endoanal magnetic resonance imaging adversely affects continence after sphincteroplasty

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Background: There is still considerable debate about the value of preoperative anorectal physiological parameters in predicting the clinical outcome after sphincteroplasty. Recently it has been reported that atrophy of the external anal sphincter can be clearly shown with endoanal magnetic resonance imaging (MRI). The aims of this study were to investigate the prevalence of external anal sphincter atrophy in women with anterior sphincter defects due to obstetric injury and to determine the impact of external anal sphincter atrophy on the outcome of sphincteroplasty.

Methods: In this prospective study, 20 consecutive women (median age 50 (range 28–75) years) with faecal incontinence due to obstetric trauma were assessed before operation with endoanal ultrasonography and endoanal MRI. The external anal sphincter was examined and evaluated for the presence of atrophy. The clinical outcome of sphincteroplasty was interpreted without knowledge of the magnetic resonance and ultrasonographic images.

Results: In all patients anterior sphincter defects could be demonstrated with ultrasonography and MRI. External anal sphincter atrophy could only be demonstrated on MRI. Eight of 20 patients had external anal sphincter atrophy. Continence was restored in 13 patients. Outcome was significantly better in those without external anal sphincter atrophy (11 of 12 patients *versus* two of eight; $P = 0{\cdot}004$).

Conclusion: External anal sphincter atrophy can only be visualized on endoanal MRI and affects continence after sphincteroplasty. Endoanal MRI is valuable in the preoperative assessment of patients with faecal incontinence.

Presented to the American Society of Colon and Rectal Surgeons in Philadelphia, Pennsylvania, USA, June 1997

Paper accepted 7 June 1999

British Journal of Surgery 1999, **86**, 1322–1327

Introduction

Childbirth is the most common cause of faecal incontinence[1]. Following primary gynaecological repair of perineal tears, persistent defects can be demonstrated in 85 per cent of patients[2]. A substantial proportion of patients with an occult sphincter defect will become incontinent with increasing age. The incidence of occult sphincter damage after childbirth was unknown until Sultan *et al.*[3] studied a consecutive group of 202 pregnant women. On endoanal ultrasonography, 35 per cent of primiparae who delivered vaginally developed a sphincter defect involving one or both muscles, which persisted at 6 months. Although sphincter defects due to obstetric trauma can be restored adequately by overlapping sphincteroplasty, incontinence persists in a substantial number of patients. The reported failure rates at long-term follow-up vary between 4 per cent[4] and 53 per cent[5].

Preoperative evaluation of patients with faecal incontinence usually includes anorectal manometry, evacuation proctography, assessment of pudendal nerve terminal motor latency and endoanal ultrasonography. The role of these preoperative anorectal function tests in predicting the outcome of sphincteroplasty is still controversial. Reports about the predictive value of these tests are numerous and conflicting.

Recently, it has been shown that endoanal magnetic resonance imaging (MRI) enables the detection of external anal sphincter atrophy[6–10] (*Figs 1* and *2*). Using conventional endoanal ultrasonography, atrophy cannot be de-

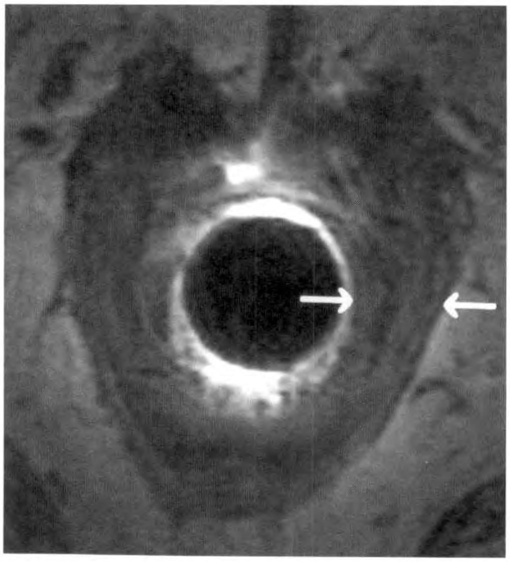

Fig. 1 Normal external anal sphincter on endoanal magnetic resonance imaging with anterior sphincter defect; arrows indicate relatively dark grey external anal sphincter

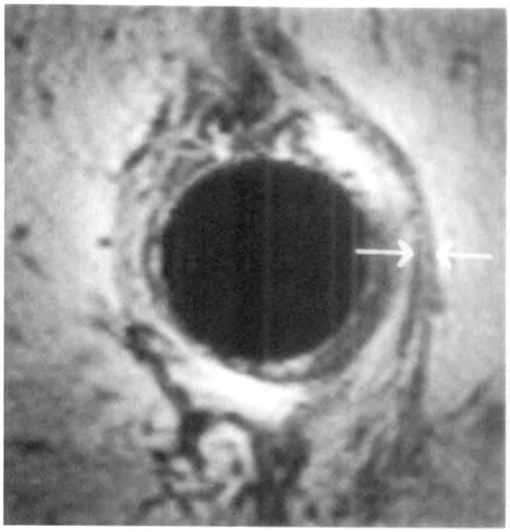

Fig. 2 Atrophic external anal sphincter on endoanal magnetic resonance imaging with anterior sphincter defect; arrows indicate relatively dark grey external anal sphincter

monstrated. The main disadvantages with MRI are the time required and the cost of an examination, which are both greater than those of endoanal ultrasonography. Therefore preoperative endoanal MRI is only justified if it influences surgical decision making or predicts final outcome. A prospective study was conducted to investigate the prevalence of external anal sphincter atrophy in women with anterior sphincter defects due to obstetric injury. The impact of external anal sphincter atrophy on the outcome of sphincteroplasty was also studied.

Patients and methods

Twenty consecutive women (median age 50 (range 28–75) years) with faecal incontinence due to obstetric trauma were assessed clinically by means of history and digital examination, and by preoperative anal manometry, endoanal ultrasonography and endoanal MRI. Both sphincters were examined and external anal sphincter atrophy was scored. Within 6 months of the preoperative assessment, all patients underwent anterior anal repair, as described earlier[11]. All repairs were performed by one surgeon (W.R.S.).

Clinical outcome was evaluated using the grade and frequency of faecal incontinence, the need for pads, the grade of social isolation and patient satisfaction after a median follow-up of 1 year. The degree of incontinence was graded as described by Parks[12]: grade I, fully continent; grade II, soiling and incontinence for gas; grade III, incontinence for liquids; and grade IV, incontinence for solid stool. Restoration of continence from grade IV to grade II or I, or from grade III to grade I, was defined as a successful outcome. Outcome was interpreted without knowledge of the magnetic resonance and ultrasonography images.

The decision to perform surgery was based solely on endosonography. MRI was considered additional and did not influence treatment.

Endoanal sonography

A Brüel & Kjaer (Naerum, Denmark) ultrasound scanner was used with a rotating probe providing a 360° image. A 7-MHz transducer, with minimum beam width of 1·1 mm and a focal length of about 3 cm, was used. Transverse images were obtained, at least at four different levels, through the anal canal.

Endoanal magnetic resonance imaging

MRI was performed at 0·5 T (Gyroscan T5-II; Philips Medical Systems, Best, The Netherlands). An endoanal coil with a diameter of 19 mm (Philips Medical Systems) was used[7–9]. Axial T2-weighted three-dimensional gradient echo and coronal and sagittal T2-weighted turbo spin-echo sequences were performed.

Determination of atrophy

External anal sphincter atrophy was assessed on hard copy by one radiologist (J.S.). To determine sphincter damage with endoanal MRI, as no criteria exist, normal endoanal MRI findings were used as a reference[7]. Atrophy of the external anal sphincter was defined as extreme thinning of its sphincter fibres or generalized fatty infiltration. The magnetic resonance images were also evaluated quantitatively using a work station with commercially available software (Gyroview HR; Philips Medical Systems). In all cases the anterior part of the external anal sphincter could not be identified because of an anterior sphincter defect. External anal sphincter width at the posterior side and at both lateral sides was determined. Furthermore, the arc of the anterior defect was noted. The area of the remaining part of the external anal sphincter was measured (*Fig. 3*). All measurements were performed on the MRI slice located at the mid-level of the anal canal, in each patient. This level of the anal canal was chosen based on normal anatomy findings using endoanal MRI[7]. At the lowest part of the anal canal, the external anal sphincter consists of two halves embedded within the ischioanal space. Cranial to this level, the two lateral halves of the external anal sphincter are connected to each other anteriorly. Just slightly more cranial to this level the external sphincter becomes completely circular, representing the mid-level, which was measured in the present study. More cranial to this level, the puborectalis muscle is first seen on endoanal MRI.

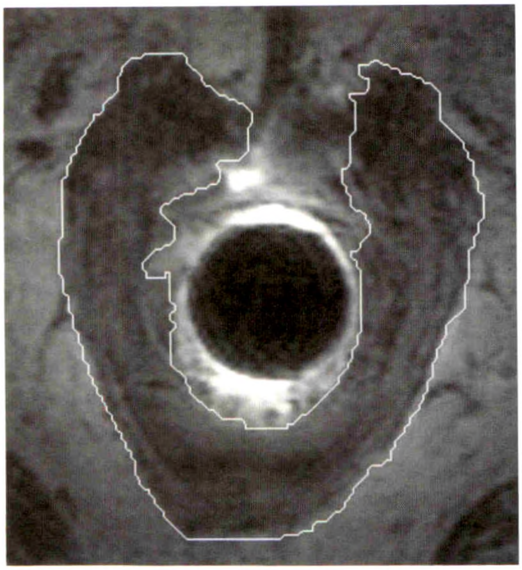

Fig. 3 Endoanal magnetic resonance imaging showing delineation of area on the image. Area is calculated by the integral software

To investigate the possibility of interobserver bias, the results of quantitative MRI assessment performed by two investigators (J.W.B. and E.R.) were compared. Each was blinded to the measurements of the other.

Statistical analysis

Fisher's exact test was used for the comparison of percentages. Mann–Whitney test was used to compare continuous data between groups. To determine agreement between measurements of different investigators, the intraclass correlation coefficient was used. $P = 0{\cdot}05$ was considered the limit of significance.

Results

In all patients anterior sphincter defects were demonstrated with ultrasonography and MRI. Qualitative or semiquantitative measurement of the thickness of the external sphincter muscle was not feasible on endoanal ultrasonography. External anal sphincter atrophy could only be demonstrated on endoanal MRI. The prevalence of external anal sphincter atrophy (determined by one of the radiologists) was 40 per cent (eight of 20 patients). Continence was restored in 13 patients. Comparing patients with and without atrophy, clinical outcome was significantly better in those without external anal sphincter atrophy (11 of 12 *versus* two of eight; $P = 0{\cdot}004$).

The MRI measurements are listed in *Table 1*. Determination of external anal sphincter width at the posterior side and both lateral sides was shown not to be useful in predicting the outcome of sphincter repair. However, there was a significant relationship between the outcome of sphincteroplasty and the arc of the external anal sphincter defect ($P = 0{\cdot}04$). Furthermore, the area of the remaining external anal sphincter was related to outcome ($P = 0{\cdot}002$). Of these two parameters, the area of the remaining external anal sphincter was the better predictor (*Table 1*).

Table 1 Magnetic resonance imaging measurements in patients with poor and good outcome after sphincter repair

	Good outcome	Poor outcome	*P*
Width (mm)			
Posterior	9·3 (2·0–23·5)	9·3 (4·7–13·1)	0·12
Left	4·3 (1·1–8·8)	2·5 (1·1–5·6)	0·22
Right	3·9 (1·1–9·0)	3·0 (1·1–6·0)	0·73
Arc (°)	55 (19–146)	85 (51–190)	0·04
Area (mm^2)	393 (121–1350)	218 (87–360)	0·002

Values are median (range). Mann–Whitney *U* test

For area of the remaining external anal sphincter, the cut-off point for successful outcome was determined. The greatest area in patients with a poor outcome after sphincteroplasty was 360 mm^2 (*Fig. 4*). Of the ten patients with an area of 360 mm^2 or less, only three had a successful outcome after sphincter repair. All ten patients with an external sphincter area greater than 360 mm^2 regained continence. A receiver operating characteristic curve was calculated for the cut-off point of area (*Fig. 5*). For a cut-off point of 300 mm^2, the sensitivity and specificity were 92 and 86 per cent respectively. For an area of 360 mm^2, they were 77 and 100 per cent.

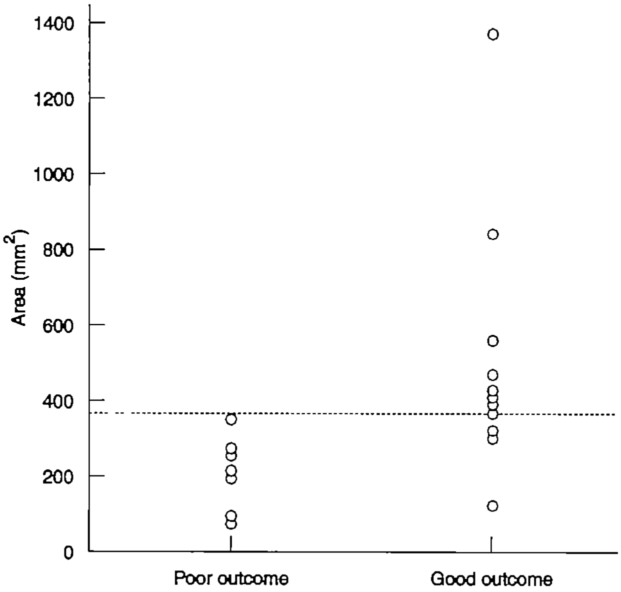

Fig. 4 Outcome of sphincter repair related to preoperative external anal sphincter area

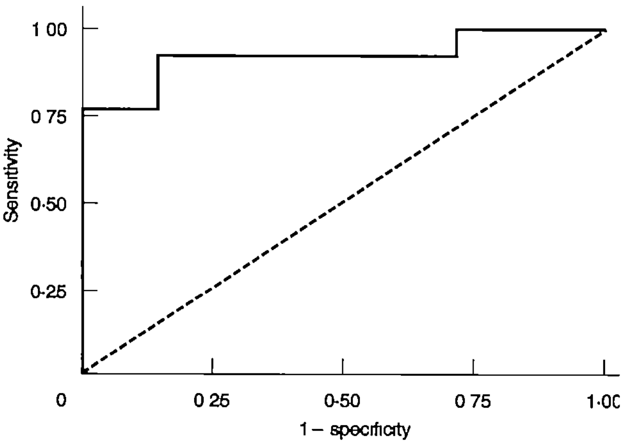

Fig. 5 Receiver operating characteristic curve (solid line) to demonstrate cut-off points of area; dotted line, base line

Atrophy, as assessed by one radiologist, and the quantitative measurement of area on MRI were well related ($P = 0·001$). In patients with atrophy, as described by the radiologist, the measured area was significantly lower than that in patients without radiological signs of external anal sphincter atrophy (214 *versus* 399 mm^2; $P = 0·001$).

Comparing the quantitative measurements of the two investigators (J.W.B. and E.R.), there was no systemic difference ($P = 0·67$). The interobserver agreement was good (intraclass correlation coefficient 0·91).

Age and surgical outcome were not related. There was also no significant correlation between age and atrophy. Furthermore, age was not related to any of the MRI measurements (width, arc or area).

Discussion

The use of conventional whole-body MRI in the evaluation of patients with faecal incontinence has been proven to be of great value in assessing patients with congenital anorectal anomalies[13]. However, anal endosonography is the imaging technique of choice for the detection of abnormalities in the region of the anal sphincters, when compared with MRI using a whole-body receiver coil[14–16]. The spatial resolution of endoanal sonography is superior to that of body coil MRI. However, a major limitation of anal endosonography is the poor inherent contrast, which makes it difficult to identify the external anal sphincter. Recently, it has been shown that the use of an endoanal coil enables the detection of anal sphincter defects as well as external anal sphincter atrophy on MRI[6,8,9] Moreover, the sensitive region of the coil extended beyond the region normally visualized with endoanal ultrasonography. In this study the value of preoperative endoanal MRI was assessed.

Anterior sphincteroplasty was found to be successful in 13 of 20 patients in the present study. This outcome is in accordance with other series[4,5]. External anal sphincter atrophy was present in eight of the 20 patients.

In 1977, Parks[17] examined biopsies of the external anal sphincter of patients with idiopathic faecal incontinence. The biopsies of all incontinent patients showed histological evidence of denervation. He therefore suggested that this type of faecal incontinence could result from denervation of muscles of the anal sphincter mechanism. This could be the result of entrapment or stretch injury of the pudendal or perineal nerves occurring as a consequence of rectal descent induced during repeated defaecation straining in constipated patients[18], or from injuries to these nerves associated with childbirth[19]. Nowadays this type of faecal incontinence is called neurogenic.

In patients with faecal incontinence due to obstetric injury both anal sphincter rupture and denervation may coexist[20–22]. Several authors have reported that denervation of the pelvic floor and subsequent failure of surgical repair can be predicted by preoperative electromyography[5,20,23–25]. In contrast, other authors were not able to confirm these findings[26–28]. Also, denervation of the external anal sphincter and its detection fade in time while the sphincter damage remains. Furthermore, electromyography of the pelvic floor is generally considered to be distressing. It seems likely that in patients with both denervation and sphincter defects, denervation of the pelvic floor will persist, regardless of the outcome of repair of the sphincter defect. It has been shown that functional results of sphincter repair in patients with neurogenic faecal incontinence are poor[29]. Therefore, in patients with both denervation and sphincter defects, a poor outcome might be expected.

If traumatic denervation leads to atrophy of the external anal sphincter, the finding of atrophy of this sphincter muscle will influence outcome after surgery. This hypothesis was confirmed by the present study. Outcome was significantly better in those without external anal sphincter atrophy. The area of the remaining external anal sphincter on endoanal MRI appeared to be of significant value in identifying patients with a favourable outcome. The objective quantitative measurement of this area was of equal value as the rather subjective determination of atrophy on hard copies of magnetic resonance images by the radiologist; the two methods were well correlated ($P = 0{\cdot}001$). The separate measurements of sphincter width at the posterior side and both lateral sides did not relate to outcome. This might be explained by the isolated value of the width measurement. The computed area consists of numerous adjacent sphincter width measurements, thereby overcoming the effect of sphincter irregularity. Determination of the presence of atrophy on endoanal MRI may enable the prediction of outcome after sphincteroplasty. Patients below the cut-off area (360 mm^2) are less likely to benefit from sphincter repair. Confirmation of this cut-off value in another group of patients is necessary.

Endoanal MRI is the first imaging technique to predict functional outcome after sphincter repair. Moreover, it directly enables the detection of external sphincter atrophy, rather than assuming atrophy by detection of pelvic floor denervation assessed by either electromyography or pudendal nerve terminal motor latencies. The authors advocate the inclusion of endoanal MRI in the preoperative work-up of patients with faecal incontinence to help predict the outcome of surgery in individual patients.

The alternatives for patients with persistent faecal incontinence after sphincteroplasty are either creation of a stoma or dynamic gracilis plasty. Since dynamic gracilis plasty is technically easier in patients in whom previous attempts to restore continence (i.e. sphincteroplasty) have not been made, selection of patients is preferable. Therefore, patients with external anal sphincter atrophy as seen on endoanal MRI might be candidates for dynamic gracilis plasty in the first place.

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Original article

Frequency of early colorectal cancer in patients undergoing colonoscopy

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Background: Early colorectal cancer is defined as carcinoma limited to the mucosa or submucosa. Up to 20 per cent of all colorectal cancers treated in some Japanese institutions are early cancers. These cancers are sometimes flat or depressed, and may be less than 1 cm in diameter. The aim of this study was to identify the frequency and morphology of early colonic cancers detected at colonoscopy by a surgeon aware of and looking for such lesions.

Methods: A review was made of all colonoscopies performed by or under the supervision of a single endoscopist between 1990 and 1998. Follow-up and outcome of all patients with early colorectal cancer was undertaken.

Results: Ninety-five invasive colorectal cancers were identified from 2198 colonoscopies. Eighteen were early colorectal cancers (T_1). Macroscopically these were flat (nine tumours), villous (four) and pedunculated (five). Two patients had lymph node metastasis. The median size of flat cancers was 20 (range 9–30) mm. Median follow-up was 3 years. One patient had local recurrence, and another, whose early cancer was metachronous, died from metastatic cancer.

Conclusion: This study identified early colonic cancer with similar frequency and morphology to that reported by the Japanese. Colonoscopy should be considered as the investigation of choice for patients with large bowel symptoms.

Paper accepted 26 May 1999

British Journal of Surgery 1999, **86**, 1328–1331

Introduction

Early colorectal cancer is defined as carcinoma limited to the mucosa (tumour *in situ* (T_{is})) or submucosa (T_1)[1] and carries a 5-year survival rate of 97·6 per cent[2]. The rate with which such lesions are detected in the UK is not known. In Japan, Shida *et al.*[3] have reported that T_1 tumours account for 22 per cent of asymptomatic screen-detected cancers, whereas Kitamura and co-workers[4] stated that 18·3 per cent of all cancers treated in their institution between 1990 and 1994 were T_{is} or T_1 lesions.

The macroscopic appearance of early colonic cancer has been classified comprehensively by Japanese endoscopists[5]. They have shown that, as well as classical polyps, early cancers can arise from flat adenomas and even occur as flat or depressed lesions with no residual adenomatous elements, raising the possibility that some cancers may develop *de novo*. There have been no UK studies of colonoscopic detection and morphology of early colorectal cancer, although a Japanese endoscopist working in Leeds has demonstrated small flat adenomas and flat cancers in British patients[6]. This paper presents experience of early colonic cancer identified at colonoscopy from routine clinical practice.

Patients and methods

Reports from all colonoscopic examinations performed on a single consultant surgeon's routine weekly list from 1990 to March 1998 were reviewed. All colonoscopies were performed by the consultant or trainees under his supervision. Before 1996 examinations were performed with fibreoptic Olympus CF10L or CF20HL endoscopes (Keymed, Livingston, UK), after 1996 Olympus CF230L videoendoscopes were used. Bowel preparation was with Klean-prep (Norgine, Harefield, UK) (four sachets) or Picolax (Ferring, Langley, UK) (two sachets), with Senna (three 7·5-mg tablets) on the day before the examination. Sedation was intravenous with 6 mg midazolam and 20 mg hyoscine butylbromide. Magnifying endoscopes or chromoendoscopy with indigo carmine dye were not used. Histological reports from all biopsies, polypectomies and related surgical resections were obtained. An independent pathologist reviewed all intramucosal carcinomas (T_{is}) to exclude the presence of submucosal invasion. As there is considerable disagreement between Western and Japanese pathologists concerning the pathological criteria used to diagnose these lesions[7], they were excluded from the study.

Morphological assessment of the T_1 cancers was obtained from the description given at endoscopy and the macroscopic appearance at pathological examination. The tumours were classified into pedunculated, villous and flat forms based on the presence of a stalk and the height of the lesion in relation to the normal mucosa, in a manner similar to that described by Kudo[5]. Case notes of patients with early cancer were then reviewed to obtain treatment, follow-up and outcome data.

Results

During the study period 2198 colonoscopies were performed, the indications for which are shown in *Table 1*. Ninety-five invasive tumours, four intramucosal carcinomas and 591 polyps were identified.

Eighteen (19 per cent) of the 95 invasive cancers found at colonoscopy were T_1 lesions. Sixteen were discovered in patients with large bowel symptoms and two were found in patients who had had a previous colonic cancer. Morphologically nine were flat, four were villous and five pedunculated. Five were in the rectum, two at the rectosigmoid junction, seven in the sigmoid, three in the transverse colon, while one was at the caecum. Of the flat cancers three were elevated, five depressed and one lateral spreading. *Figs 1* and *2* show the typical appearance of a flat depressed cancer macroscopically and histologically. Their median size was 20 (range 9–30) mm, and three were 10 mm or less.

All patients with flat or villous lesions underwent surgical resection. Patients' ages ranged from 60 to 87 (median 77) years. Three had local resection only, one had colotomy and local resection of a villous lesion, and two with rectal lesions had transanal excision. Three of the five patients with pedunculated cancers underwent colectomy, and the remaining two were treated by snare diathermy alone.

Two of the surgically resected specimens showed lymph node metastasis; one was a 28-mm flat, depressed, moderately differentiated carcinoma whereas the other was a 30-mm well differentiated mucin-rich carcinoma arising in a severely dysplastic tubulovillous adenoma. Both extended deeply into submucosa, although neither showed local invasion of lymphatics. Median follow-up of the patient population was 3 (range 0·5–6) years, and 11 patients were followed for 3 years or longer. There has been one local recurrence at 2 years following transanal resection, which was again treated by local excision owing to the patient's poor health. One patient with a metachronous

Table 1 Indications for colonoscopy

Indication	No. of patients
Any bowel symptom	1273 (58)
Previous polyp or cancer	478 (22)
Family history	63 (3)
Anaemia	117 (5)
Inflammatory bowel disease	91 (4)
Other or not specified	176 (8)
Total	2198 (100)

Values in parentheses are percentages

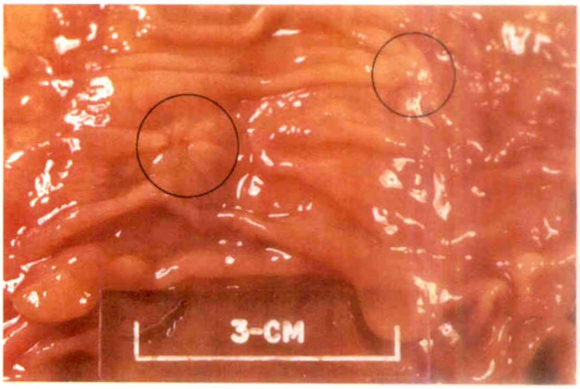

Fig. 1 Resection specimen of a 9-mm flat, depressed cancer found at videocolonoscopy in the transverse colon of a 60-year-old man (large circle). The second marked lesion (smaller circle) is a flat adenoma; note the mucosal irregularity and colour change

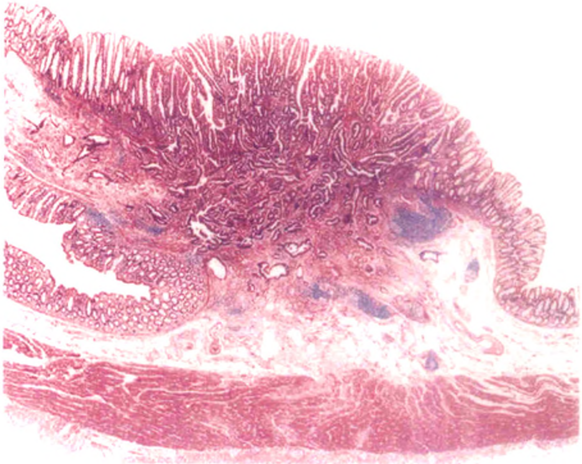

Fig. 2 Histological section of a flat cancer demonstrating submucosal invasion

early cancer died from metastatic disease; his first cancer was a $T_3 N_0 M_0$ sigmoid tumour resected 2 years previously.

Discussion

This study demonstrated a similar frequency (19 per cent) for early colorectal cancer in patients undergoing colonoscopy to that reported by the Japanese[4]. Approximately two-thirds of the colonoscopies were performed for patients with large bowel symptoms, and one-third was carried out as a screening procedure. All the major morphological types were observed with lesions of similar size to those already reported[5,8]. Half of the early cancers were flat, with one-third of these 10 mm or less in diameter. Recognition of these lesions did not require specialized techniques, rather a high suspicion for areas of mucosal irregularity, depression or altered colour as well as the traditional search for polyps.

It is not known what proportion of colorectal cancers detected by endoscopy in the UK are early lesions. In a recent screening study of asymptomatic patients in the UK, only 20 per cent were Dukes stage A tumours ($T_1 N_0 M_0$ or $T_2 N_0 M_0$)[9]. This compares with a Dukes stage A detection rate of 30 per cent in the present study. Interestingly this rate is similar to that reported by Kalra *et al.*[10] in a series of open-access flexible sigmoidoscopies. Colonoscopy is superior to double-contrast barium enema in detecting early colorectal cancer[11] and, as experience with colonoscopy grows, more early lesions are being detected[5,6].

Recent work has shown improved definition of mucosal abnormalities with magnifying endoscopes and indigo carmine dye[12,13]. While these techniques may give more information about the lesion, and in particular demonstrate the extent of flat lesions, the primary step is still the recognition of any mucosal abnormality at colonoscopy and the taking of appropriate biopsies. Many features of the endoscopic appearances of flat or depressed cancers have been described[5,6,12,13], including differences in pit pattern on magnifying videocolonoscopy, colour changes and areas of minute depression. At endoscopy many of these lesions look like a minicancer with central depression and elevation of the surrounding edges. A further feature found to be helpful in recognizing adenomas with areas of invasion is that at endoscopy the lesions sometimes give the impression of having burrowed submucosally at one or more of their edges.

Two of the 18 T_1 tumours in this study were found at surgical resection to be associated with lymph node metastasis. This finding is consistent with that reported in the literature[14,15]. One was pedunculated, the other flat, and both were of considerable size (28 and 30 mm) and not amenable to endoscopic resection. Nevertheless, flat lesions of up to 3 cm have been removed by endoscopic resection[5], raising the question as to whether this is appropriate treatment for early colorectal cancer. Morphologically flat tumours are significantly at risk for lymph node involvement, and the depth and pattern of submucosal invasion can also be correlated to the risk of nodal metastasis[5,15]. Additionally some authors have classified early colorectal cancer as high or low risk depending on the degree of differentiation and whether there is lymphatic invasion[14,16]. For well or moderately differentiated lesions without lymphatic invasion, the authors[16] were unable to show any difference in 5-year survival whether patients had a local or radical resection for early rectal cancer.

While selected early rectal tumours may be dealt with by a variety of methods of local resection, management of flat cancers elsewhere in the colon generally requires formal resection. If snare diathermy or endoscopic mucosal resection removes the majority of a lesion, tattooing the site to aid identification of the appropriate bowel segment for resection at laparotomy is important[17]. This will also be necessary for small flat cancers confirmed by biopsy only, as these may not be palpable at laparotomy.

This study identified early colorectal cancer at routine colonoscopy with equal frequency and similar morphology to that reported by the Japanese. Colonoscopists need to be aware that early cancers often present as flat lesions or areas of mucosal irregularity, as well as polyps. While a variety of radiological and endoscopic methods are presently being assessed, these data support the use of colonoscopy as the current method of choice for investigating patients with large bowel symptoms.

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Outcome in patients with colorectal cancer managed by surgical trainees

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Background: The surgeon is an important variable that influences outcome following colorectal cancer surgery. Operative training of suitable quality and quantity is essential if intersurgeon variation is to be reduced. The aim of this study was to examine the outcome of colorectal cancer surgery when a high proportion of the operations were performed by trainee surgeons.
Methods: A prospective 7-year (1989–1996) audit of 306 consecutive colorectal cancers referred to a single general surgeon with a colorectal interest was carried out. The outcome (anastomotic leakage, 30-day mortality rate, local recurrence and cancer-related survival) of operations performed by the consultant was compared with that of his trainees.
Results: Some 245 (92·5 per cent) of 265 patients undergoing laparotomy had a resection. Seventy (28·6 per cent) and 67 (27·3 per cent) of operations were performed by supervised and independent trainees respectively. There was no difference between the consultant, supervised and independent trainees for 30-day mortality rate (6·5, 6 and 4 per cent respectively), clinical anastomotic leakage rate (9, 2 and 5 per cent) and local recurrence rate (2, 3 and 7 per cent). There was no difference between the three groups for adjusted 5-year disease-related survival rates.
Conclusion: Properly supervised trainees can resect a high proportion of colorectal cancers without compromising immediate outcome or long-term survival.

Presented in part to the annual meeting of the Association of Surgeons of Great Britain and Ireland, Bournemouth, UK, April 1997, and published in abstract form as *Br J Surg* 1997; 84(Suppl): 56

Paper accepted 4 June 1999

British Journal of Surgery 1999, **86**, 1332–1336

Introduction

Surgery is the principal treatment for colorectal cancer. There is a substantial body of evidence suggesting that the surgeon is an important variable that influences outcome following colorectal cancer surgery[1–3]. Operative training of suitable quality and quantity is essential if the outcome of colorectal cancer is to be improved. However, if trainees undertake a larger proportion of major procedures and operations for cancer there will be concern that patient outcome may be compromised. In a recent systemic colorectal cancer review, the National Health Service Centre for Reviews and Dissemination was unable to locate any training study that had adjusted adequately for case mix[4].

The aim of this study was to examine the immediate and long-term outcome following colorectal cancer surgery in a unit where more than half of the procedures were performed by trainee surgeons.

Patients and methods

Details of all patients with colorectal cancer referred to a single consultant (R.J.A.) were recorded prospectively on a microcomputer (Macintosh; Apple, Cupertino, California, USA) using a bespoke database (FileMaker; Claris, Santa Clara, California, USA). All appropriate clinical, operative, pathological and follow-up data were recorded. As part of the study one author (K.K.S.) randomly selected the case notes of 78 patients (25·5 per cent) and independently compared these against the database.

The outcome benchmarks used to compare trainees and their consultant were 30-day postoperative mortality, anastomotic leakage, local recurrence and disease-related survival rates.

Definitions

A supervised operation was one in which the consultant was scrubbed. No supervision was assumed if the consultant was elsewhere in the theatre complex or called to offer advice but did not scrub. If the trainee undertook only a part of the operation, the surgeon resecting the bowel containing the cancer was considered the principal surgeon. If the senior assistant 'took over' the operation, that surgeon was credited with the operation. Abdominoperineal resections were credited to the surgeon performing the abdominal resection.

The aim of the operation was a radical anatomical resection using precise sharp dissection, as described previously[5,6]. Resections were considered curative unless there were either multiple liver metastases, biopsy-proven single liver metastasis, a perforated cancer or biopsy-proven histological evidence of local residual cancer[7].

Postoperative mortality was a death occurring within 30 days of operation.

Rectal cancers were within 16 cm of the anal verge. If an anterior resection was performed, the mesorectum was divided at least 5 cm distal to the tumour, but a total mesorectal excision was performed only for low tumours (within 6–8 cm of the anal verge)[8]. After cross-clamping, the distal rectum was routinely washed out with aqueous povidone–iodine.

The duration of follow-up was calculated from the date of operation to the date of last review or of death. Patients were considered free from cancer if the clinical assessment, including sigmoidoscopy if appropriate, was normal. Patients with rectal cancer remained under hospital follow-up for at least 5 years. Although most patients with colonic cancer remain under hospital follow-up, a small number of elderly or frail patients were discharged to the care of their general practitioner (GP) after 2 years. Follow-up for these patients was obtained annually from the GP and the patient. Routine colonoscopy was performed 1 and 5 years after resection. Radiological investigations were undertaken if there was clinical suspicion of recurrent disease or if the carcinoembryonic antigen level became raised (greater than 70 U/l). Local recurrence was any recurrent disease in the operative field.

Statistical analysis

All tabulations and analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA). Comparisons between grades of surgeons in respect of postoperative death, anastomotic leak and local recurrence were made using the stratified χ^2 test. Recurrence-free survival for each Dukes stage was estimated with Kaplan–Meier survival techniques[9]. Significant predictive factors for survival were identified using the Cox proportional hazards model[10]. These factors were then incorporated into models comparing surgeon grade. Results were reviewed by an independent statistician.

Results

Between November 1989 and November 1996, 306 consecutive patients were referred with a first colorectal cancer. Surgical intervention was either not possible or inappropriate in 23 patients (7·5 per cent). The cancer was managed without laparotomy in 18 (5·9 per cent). The remaining 265 (86·6 per cent) underwent a laparotomy; 245 (92·5 per cent) had a resection and of these 213 (86·9 per cent) were considered curative.

Of the 245 patients who underwent resection, 120 (49·0 per cent) were male. Mean age was 71 (range 36–95) years. Dukes classification following resection was: stage A in 38 patients (15·5 per cent), stage B in 107 (43·7 per cent), stage C in 68 (27·8 per cent) and stage 'D' (palliative resection) in 32 (13·1 per cent). Ten of 35 patients undergoing emergency operation had a palliative resection, compared with 22 (10·5 per cent) of 210 patients having an elective resection ($\chi^2 = 10{\cdot}30$, 1 d.f., $P = 0{\cdot}016$). Twenty-eight trainees performed 137 resections (55·9 per cent) (*Table 1*).

Adjuvant radiotherapy was given to nine patients (one preoperative) having a curative rectal resection. Six of these patients had an abdominoperineal resection. Adjuvant postoperative chemotherapy was given to seven patients.

Immediate outcome

There were 14 (5·7 per cent) postoperative deaths: five after emergency operation ($n = 35$) and nine after an elective operation ($n = 210$). Seven deaths (6·5 per cent) followed an operation by the consultant, four (6 per cent) by a supervised trainee and three (4 per cent) by an independent trainee ($\chi^2 = 0{\cdot}30$, 2 d.f., $P = 0{\cdot}85$).

A clinical anastomotic leak occurred in 12 (5·4 per cent) of 222 resections with an anastomosis: one after resection of the right colon ($n = 82$), three after resection of the left and sigmoid colon ($n = 60$) and eight after resection of a rectal cancer ($n = 80$). There were no differences between the three groups (leakage rates of 9, 2 and 5 per cent respectively for consultants, unsupervised and independent trainees; $\chi^2 = 3{\cdot}67$, 2 d.f., $P = 0{\cdot}15$). Anterior resections for rectal cancer performed by the consultant were more likely to be

Table 1 Supervised training

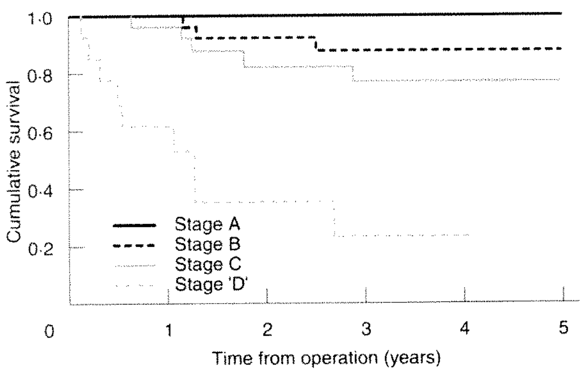
	Right colon	Left colon	Rectum			Total
			APR	AR	Other†	
Consultant	26	32	9	39	2	108 (44·1)
Supervised trainee*						
Senior registrar	6	5	2	19		32 (13·1)
Registrar	5	9	3	10		27 (11·0)
SHO	9	1	1	0		11 (4·5)
Subtotal	20	15	6	29		70 (28·6)
Independent trainee						
Senior registrar	22	12	1	9		44 (18·0)
Registrar	11	5	0	2	1	19 (7·8)
SHO	3	1	0	0		4 (1·6)
Subtotal	36	18	1	11	1	67 (27·3)
Total	82	65	16	79	3	245 (100·0)

Values in parentheses are percentages. In 15 of 16 abdominoperineal resections (APRs) the consultant was the perineal surgeon. *Supervised by consultant. †Three patients (Hartmann procedure, 2; segmental resection, 1) had a palliative resection. AR, anterior resection; SHO, senior house officer

Table 2 Local recurrence, with or without distal recurrence, after curative resection

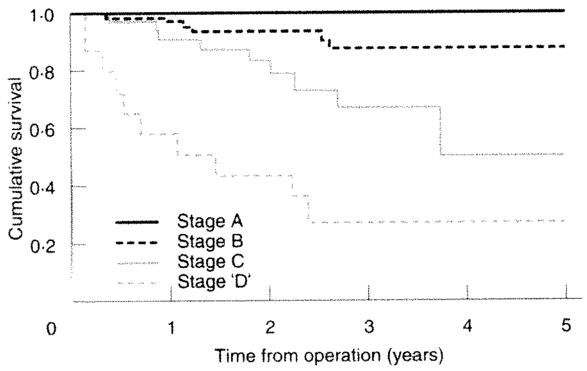
	Right colon	Left colon	Rectum	Total
Consultant	0 of 23	0 of 27	2 of 44	2 of 94 (2)
Supervised trainee	0 of 19	1 of 14	1 of 30	2 of 63 (3)
Independent trainee	4 of 30	0 of 16	0 of 10	4 of 56 (7)
Total	4 of 72 (6)	1 of 57 (2)	3 of 84 (4)	8 of 213 (3·8)

Values in parentheses are percentages



No. at risk						
A	21	21	17	11	7	4
B	28	27	25	19	13	11
C	24	24	21	15	12	8
'D'	13	12	6	3	2	

Fig. 1 Cumulative-disease related survival by Dukes stage following resection for rectal cancer. Deaths within 30 days were excluded



No. at risk						
A	12	10	8	6	3	2
B	63	61	52	35	20	12
C	35	33	24	14	6	3
'D'	15	14	8	5	2	2

Fig. 2 Cumulative disease-related survival by Dukes stage following resection for colonic cancer. Deaths within 30 days were excluded

in male (25 of 39 *versus* 20 of 40 for trainees), an emergency (three of 39 *versus* 0 of 40), and the tumours were more likely to be below 8 cm (17 of 39 *versus* 11 of 40) and tethered or fixed (11 of 39 *versus* six of 40).

Recurrence and survival

The minimum elapsed time from operation was 24 months. One patient was lost to follow-up after resection of colonic

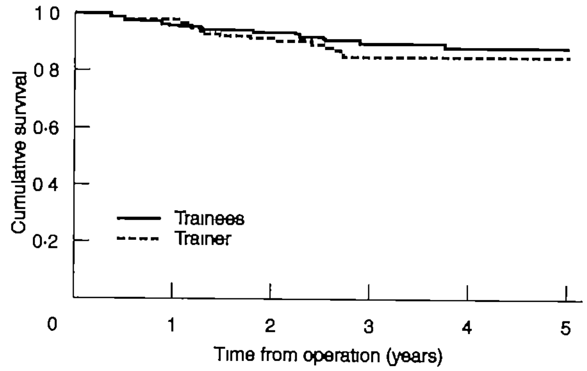


Fig. 3 Adjusted disease-related survival for trainees and the consultant. Deaths within 30 days were excluded

cancer. The overall local recurrence rate, with or without distal recurrence, was eight (3·8 per cent) of 213 curative resections (*Table 2*).

The unsupervised trainees responsible for the four local recurrences following resection of a right colonic carcinoma stated that these resections were locally palliative. Their subjective impression appeared to be confirmed by the histological findings (pT_3 ($n = 2$) and pT_4 ($n = 2$)). However, biopsies were not taken to confirm there was residual cancer[7] so these resections were classified as curative. One rectal local recurrence occurred after an anterior resection that leaked, another after an intraoperative tumour perforation which was then complicated by an anastomotic leak, and the third after an abdominoperineal resection.

Recurrence-free survival for rectal and colonic resections was initially analysed by Dukes stage (*Figs 1* and *2*). Patients staged as Dukes 'D' and still alive at 2 years either had a perforated cancer or histopathological biopsy showing disseminated or local residual cancer at the time of operation. The log rank test was used to make statistical comparisons between Kaplan–Meier survival estimates. Survival outcome was significantly influenced by Dukes stage. There was no statistical difference when analysed by the grade of operating surgeon (consultant or trainee).

The independent risk factors for survival identified by the Cox proportional hazards model were Dukes stage and tumour differentiation. The grade of the surgeon was not an independent significant factor affecting survival outcome (*Fig. 3*).

Discussion

In this study there was no difference in outcome between the trainees and their consultant. Although trainees undertook more than half the operations, the overall outcome was comparable with that in personal series in which almost all the operations were undertaken by the consultant[11–13]. This suggests that with appropriate training and supervision surgical trainees can safely undertake a high proportion of colorectal cancer resections without compromising patient care. However, trainees require 50–70 per cent more time than consultants[14]. The inevitable conflict between service and training can be resolved only by the provision of adequate and dedicated training resources.

This finding is in keeping with two recent reports in which a high proportion of upper gastrointestinal resections and carotid endarterectomies was undertaken by appropriately trained or supervised trainees without compromising patient care[15,16]. These are important observations given the profession's recent efforts to improve surgical training and the increasing worldwide emphasis on quality in healthcare provision[17–19].

The outcome after rectal surgery is of particular interest. The trainees were clearly not specialists and individually would be considered low-volume surgeons. The senior author (R.J.A.) has visited Heald and attended his 'master-classes'. That he and his trainees subsequently achieved similar results, as have others[20] who were tutored directly by Heald, suggests that intersurgeon variation after rectal cancer surgery may have been secondary to the principles of the surgical technique used rather than to intrinsic differences in individual surgeon ability. This study confirms previous reports which have noted that a low local recurrence rate after rectal surgery may improve the subsequent cancer-related survival rate by up to 20 per cent.

The anastomotic leak rate following anterior resection of rectal cancer is in keeping with that of other studies. The majority occurred early in the series and this may reflect the senior author's learning curve with total mesorectal excision. The leak rate has subsequently fallen with the greater use of a defunctioning ileostomy and coloanal pouch[21].

In this study 28·6 per cent of all resections, and 51·1 per cent of those undertaken by trainees, were consultant supervised. The comparative figures in the first 4 years of the Lothian and Borders Large Bowel Cancer Project were 13·9 and 31·5 per cent respectively. This was a higher proportion than that in other contemporary UK colorectal cancer audits (7·6 and 17·4 per cent respectively)[19]. These UK audits suggest that, in absolute numbers, the average specialist registrar undertaking a right hemicolectomy (the basic large bowel training operation) would be assisted by a consultant less than twice. If all elective anterior resections were undertaken by trainees who were specialist registrars in their fifth or sixth years, they would, on average, be assisted by a consultant less than twice. In the USA, where trainees are supervised during most operations, residents undertaking a 1-year colorectal fellowship would personally expect to perform over 100 large bowel resections[22].

Critics might argue that, as this was not a randomized study, the similar outcome might be due to patient selection. Undoubtedly there was patient selection and this is inevitable, indeed desirable, in a properly structured training programme. For example, the same operation might be suitable for an unsupervised senior trainee or a supervised intermediate trainee, but not for a junior trainee even if supervised. The senior author and two consultant colleagues worked as a single combined unit, and a trainee of appropriate experience was usually available whatever the complexity of the case. In future, successful training programmes must be flexible enough to ensure that whatever the complexity of the individual case there will be trainees present to undertake that part of the operation appropriate to their experience.

In conclusion, this study suggests that trainees can resect a high proportion of colorectal cancers without compromising outcome. However, this requires close consultant supervision, which will have important service implications.

Acknowledgements

The authors gratefully acknowledge the help of Ms Pauline Ralston, Senior Statistician, in the statistical analysis.

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Original article

Treatment of persistent pruritus ani in a combined colorectal and dermatological clinic

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Background: Pruritus ani is a common and socially embarrassing condition which is often poorly managed. It is often classified as idiopathic where the symptoms are usually transitory or secondary when a more persistent itch is experienced. The aim of this study was to establish the cause of pruritus ani in a group of patients referred to a combined colorectal and dermatological clinic, and to determine the most appropriate treatment.

Methods: Forty consecutive patients with pruritus ani were referred over a 6-month period from either the general practitioner or another hospital consultant to a combined colorectal and dermatological clinic. They were assessed by history, completion of a general health questionnaire, full examination of the skin, digital rectal examination, proctoscopy, sigmoidoscopy and patch testing. Patients were treated according to clinical findings at assessment.

Results: Thirty-four patients had a recognizable dermatosis, three had superficial perianal fissuring and three had a normal perineum; two required surgical intervention. Eighteen patients had a positive reaction when patch tested. All patients have shown an improvement or complete resolution of symptoms with treatment.

Conclusion: This series has shown that the majority of patients presenting with pruritus ani have a dermatosis as the underlying cause of their symptoms and that many of them have developed contact sensitivities to the various topical medications used. These findings suggest that referral to a dermatologist in the first instance may be more appropriate.

Paper accepted 27 May 1999

British Journal of Surgery 1999, **86**, 1337–1340

Introduction

Pruritus ani is defined as an itch localized to the anus and perianal skin and is usually a symptom of an underlying disorder of the epithelium in that area or of anorectal pathology. Persistent pruritus ani is a poorly managed, common and socially embarrassing condition. When no demonstrable cause is found, it is often described as idiopathic and general advice regarding hygiene is given which only results in relief for the minority[1].

This prospective study attempts to establish the cause of pruritus ani in patients referred to hospital.

Patients and methods

Forty-one patients referred to the Department of Surgery with pruritus ani were recruited. A combined colorectal–dermatological clinic was established for a 6-month period which was held every fortnight to see these patients.

A history was taken according to a pro forma which included a history of the complaint, any change in bowel habit and details of any other previous or current dermatological or gastrointestinal problems. The patients were also asked to complete a general health questionnaire (GHQ 28).

Investigation included a full examination of the skin, digital rectal examination, proctoscopy and sigmoidoscopy, and all patients were offered patch testing at a later date using the European standard series with an extended perianal battery.

Results

History and physical examination

Of the 41 patients referred, 40 had pruritus ani. The remaining patient had been incorrectly referred to the clinic with a main complaint of vulval pain and not pruritus ani as stated in the referral letter.

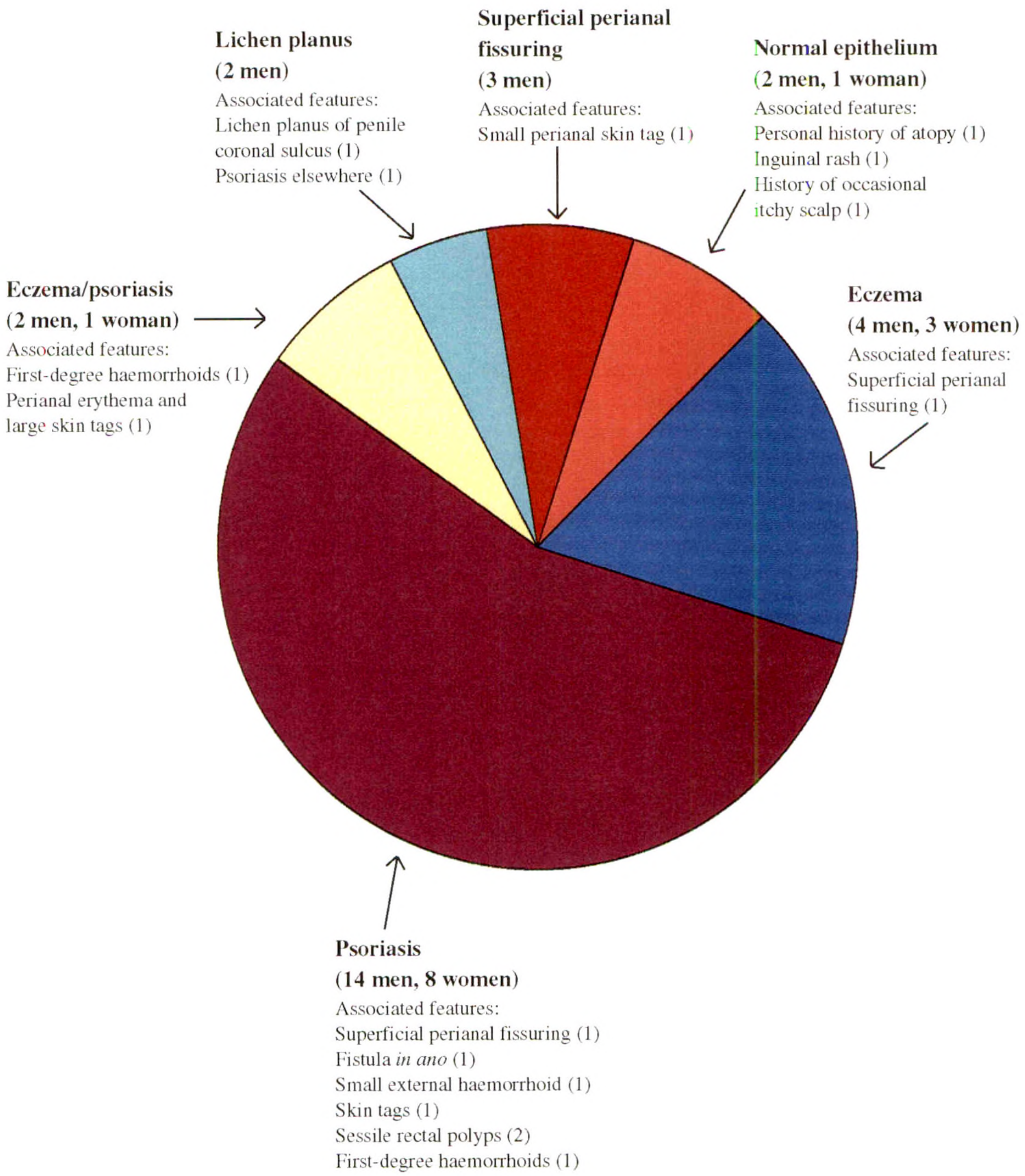

Fig. 1 Findings on clinical examination ($n = 40$)

Twenty-seven of the 40 patients were men and 13 were women. The median age was 42 (range 18–78) years. Thirty-three of the 40 patients were referred from the general practitioner, ten of whom had been referred to a hospital specialist in the past with a similar problem. The remaining seven had been seen by either a dermatologist or a general surgeon before referral to the combined clinic. The majority of these patients had already been screened for or treated blindly for threadworms *(Enterobius vermicularis)* before referral. The remaining two patients proved negative on subsequent testing using adhesive tape.

Symptoms reported by the patients included perianal itch alone in 25, itch and pain in 11, and perianal pain alone in four. The median duration of symptoms was 3 years (range 2 months to 41 years). The findings on physical examination are shown in *Fig. 1*.

Patch testing

Patch tests were performed in 32 patients as eight declined this investigation. They were tested against the European standard series, a steroid series and a topical medicament series. Eighteen of the 32 had positive patch tests. Positive reactions were found in all patient groups and this probably reflects the numerous topical treatments applied previously. The majority of these were not thought to be clinically relevant as all but one of the patients had ceased to be in contact with preparations containing the relevant allergens. The only patient who may have had a relevant result was sensitive to 1 per cent para-phenyl diamine). He did not have dyed hair but his wife did. She shampooed her hair in the bath water which the patient later bathed in. His only clinical finding was some superficial perianal fissuring. Once his wife stopped shampooing her hair in the bath, his symptoms resolved.

General health questionnaire

All patients completed a general health questionnaire (GHQ 28). Three of the 40 questionnaires were incorrectly completed and were therefore not included. Five of the remaining 37 scored above the threshold of 7/8.

Treatment

All patients were advised on the use of aqueous cream or emulsifying ointment as a soap substitute, were advised on avoidance of soap and bubble baths, and instructed not to shampoo their hair in the bath.

A topical steroid was prescribed in all patients with a dermatosis. The steroid prescribed varied in potency from 1 per cent hydrocortisone to clobetasol proprionate ointment depending on the severity and degree of lichenification. The steroid ointment was applied once at night with instruction that a 30-g tube should last for 3–6 months.

Once the symptoms had resolved, the patients were advised to discontinue the steroid application but to continue with the soap substitute. The steroid ointment could be used again if symptoms returned. In the three patients with no perianal skin changes, aqueous cream was advised as a soap substitute to help with the itch and 5 per cent lignocaine ointment was prescribed if there was the additional symptom of pain. No topical steroid was used in these patients.

In the first instance no treatment was given for any of the first-degree haemorrhoids seen on proctoscopy. One deep fissure *in ano* was treated conservatively with intralesional triamcinalone injections (10 mg/ml) with a good response. Two patients were referred for surgery, one for laying open of a fistula *in ano* and the other for excision of large perianal skin tags. On histological examination of these tags, there was no granulomatous change.

Patients were all seen for follow-up at the time of patch testing and all had reported improvement or complete resolution of symptoms. The two patients with lichen planus had further follow-up in the dermatology clinic.

Discussion

In this series 34 of 40 patients presenting with pruritus ani had an underlying dermatosis which accounted for their symptoms, the commonest being psoriasis. Over half of the patients patch tested had positive reactions. Ten of those with signs of psoriasis and four of those with signs of eczema had a positive patch test. Only two patients had anorectal pathology requiring operation while the remainder reported an improvement in symptoms or complete resolution with medical management.

Pruritus ani is often classified as being idiopathic[1] which is more often associated with transient and intermittent symptoms[2,3]. Suggested exacerbating factors include diet (e.g. coffee, tea, dairy products, chocolate, tomatoes), poor personal hygiene/soiling and stress[1,2,4–9]. Patients with secondary pruritus ani generally have more persistent symptoms, usually with an identifiable cause. Dermatological conditions can be the underlying problem and the perianal skin may be the only site affected[1].

The incidence of benign or malignant anorectal conditions associated with pruritus ani has varied between previous studies. Smith *et al.*[1] found prolapsing internal haemorrhoids in eight (11 per cent) of 75 patients. In this series, 25 per cent of patients had benign anorectal pathology. Daniel *et al.*[10] not only found benign pathology in 50 per cent of patients but also found coexisting anorectal neoplasia in 16 per cent. In the present series no anorectal neoplasia was found. This may be a reflection of the different median age at presentation (42 *versus* 52 years in Daniel's series).

Contact sensitivity may be an important factor in pruritus ani[11–14]. Eighteen of 32 patients in this series had positive patch tests, with fragrance mix, preservatives and topical antibiotics being the commonest allergens. Only three were nickel-sensitive and no patient was sensitive to local anaesthetics.

The General Health Questionnaire has been used to identify potential cases of psychiatric illness[15,16] and the threshold score of 7/8 has been found to be particularly sensitive and specific[17]. Anxiety and depression are often quoted as aggravating factors for pruritus ani[18] but in this series only five of the 37 patients scored above the threshold.

This study has shown that the majority of patients with long-standing pruritus ani had an underlying dermatosis. Patch testing is an important part of the investigation of these patients as there is a high incidence of sensitization to previously used topical preparations as shown in this series.

Contact sensitivity may therefore aggravate the condition and increased patient awareness of potential allergens will help in their future management.

The findings of this study suggest that patients with long-standing pruritus ani with no other symptoms to suggest colorectal pathology should be referred to a dermatologist for assessment and patch testing.

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Original article

Prospective study of primary anastomosis without colonic lavage for patients with an obstructed left colon

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Background: Traditionally, left-sided colon obstruction is managed by a multistaged defunctioning colostomy and resection. However, there is growing acceptance of one-stage primary resection and anastomosis with on-table antegrade irrigation. This paper presents a series of patients managed prospectively by primary anastomosis without intraoperative colonic lavage.
Methods: Emergency resection of acutely obstructed left-sided colonic carcinomas was performed. This was followed by primary anastomosis without on-table lavage after bowel decompression using a new technique.
Results: Fifty-eight consecutive, unselected patients underwent bowel decompression, resection and primary colocolic anastomosis. Only one patient developed a leak at the anastomotic site, requiring pelvic abscess drainage and transverse loop colostomy. One death occurred 12 h following surgery. Autopsy confirmed that this was due to myocardial infarction. Mean hospital stay was 9·8 days.
Conclusion: Emergency surgery on the obstructed left colon can be carried out safely after decompression alone, without intraoperative colonic lavage.

Paper accepted 28 May 1999

British Journal of Surgery 1999, **86**, 1341–1343

Introduction

Although left-sided colonic obstruction is often managed by the traditional method of staged defunctioning colostomy and resection, there has been a trend towards one-stage primary resection and anastomosis[1–5]. This is now widely regarded as a safe alternative to the other multistaged options, even in the elderly[6,7]. However in all these reported series, on-table antegrade colonic irrigation was performed to decompress and clean the proximal obstructed colon. While decompression may be desirable (to decrease distension, facilitate abdominal closure and improve colonic blood supply), there is some evidence that complete cleaning of the colon of faecal matter is not necessary for ensuring anastomotic integrity[8,9]. Both Hsu[10] and Nyam *et al.*[11] have suggested that decompression without lavage is safe but in neither series was the decompression performed very early in the procedure and neither study was prospective.

In this centre, over the past 9 years antegrade irrigation has been abandoned in favour of a novel technique of proximal decompression alone before anastomosis. The bowel is decompressed long before the mesentery is divided and the tumour resected. The authors' experience with 58 consecutive patients treated in this fashion is now reported.

Patients and methods

From October 1989 to June 1998, 58 consecutive patients with acute intestinal obstruction due to left-sided colonic lesions were operated on by the authors (of registrar and consultant grade) using the procedure described below. No patient was excluded and Hartmann's procedure was not performed.

All patients were given perioperative antibiotics, ampicillin/clavulanic acid 1·2 g or ceftriaxone 2 g with metronidazole 500 mg intravenously, every 8 h, depending on availability. The antibiotic regimen was administered for 24 h only. Wounds were inspected at 5 and 10 days after operation and again at 4 weeks. Wound infection was defined as serous or purulent discharge occurring at any time during observation. Anastomotic dehiscence was diagnosed on clinical grounds alone.

At laparotomy, the obstructing lesion and adjacent colon were mobilized for resection. Before division of the mesentery, its vessels or the gut, a 10-cm segment of distended colon immediately proximal to the obstructing lesion was emptied of its contents by manually milking it proximally and placing a crushing (e.g. Kocher's) clamp across the colon. A purse-string suture was placed in this 10-cm collapsed segment of bowel (between the crushing clamp and the obstructing lesion) and a 36-Fr chest tube was inserted via a colotomy secured by the purse-string suture.

Gentle suction was applied to the chest tube as the crushing clamp was removed and the chest tube slid proximally into the obstructed distended colon. The colon decompressed rapidly and easily since it was distended mostly with gas and liquid faecal matter. Although some attempt was made to milk air and fluid from the distended proximal colon as the chest tube was advanced, no effort was spent in ensuring near complete colonic emptying, even if bits of solid faecal matter were present. It was very unusual for this multiperforated 36-Fr chest tube to become blocked but if this did occur the tube was flushed with a bladder syringe of saline. After rapid decompression of the colon (mean duration 12 (range 7–18) min), the chest tube was withdrawn and the purse-string suture tied. Division of the mesentery, colon resection and primary anastomosis were then performed, the purse-string being included in the specimen. In the short period between decompression and anastomosis the bowel wall at the resection margin appeared well vascularized, healthy and relatively normal (not thin walled or friable). The entire two-layered anastomosis was completed using an inverting suture technique so that no mucosa pouted after the initial full-thickness layer was completed. The abdomen was closed without lavage or drainage.

Results

Fifty-eight consecutive patients were studied prospectively. Age ranged from 54 to 89 (mean 63) years; there were 36 men and 22 women. The sigmoid colon was the commonest site (55 per cent), followed by the descending colon (28 per cent), distal transverse colon (10 per cent) and splenic flexure (7 per cent). All obstructing lesions were proven histologically to be adenocarcinomas.

Hospital stay ranged from 4 to 21 (mean 9·8) days. Two patients required postoperative ventilation in the intensive care unit. Neither developed anastomotic complications. One 80-year-old patient died 12 h after surgery from a myocardial infarction which was confirmed at autopsy.

The only anastomotic leak occurred in a 61-year-old woman with a sigmoid carcinoma (Dukes C). At laparotomy on day 6, a pelvic abscess adjacent to the anastomosis was drained and a proximal defunctioning transverse loop colostomy was performed. The patient recovered well and was discharged after a total of 15 days in hospital. Superficial wound infections occurred in seven patients (12 per cent); none of these required further surgery.

Discussion

While the major advantage for primary anastomosis after peroperative colonic lavage for left-sided colonic obstruction is that it is single stage, does not result in colostomy, may have lower associated morbidity and mortality rates and shorter hospitalization than the multistaged procedure, there are several drawbacks. Colonic lavage takes more time (44 min according to Forloni *et al.*[12]) than decompression (12 min). It also uses several litres of solution for irrigation and may be associated with more risk of spillage and contamination than decompression without lavage[11]. In a third world setting, disposable drainage bags or sterile anaesthetic elephant tubes may not be readily available in an emergency. Moreover, recent evidence shows no clear association between failure to clean the colon thoroughly and anastomotic dehiscence[8,9,13].

The present series supports the view that complete cleaning of the proximal colon of all faecal residue is probably unnecessary. However, decompression of the colon is recommended as this facilitates closure of the abdomen and may actually improve the blood supply and tone of the decompressed gut wall. The 36-Fr chest tube is multiperforated and has a wide bore so, while freely draining the bowel gas, it is less likely to become blocked by the thick liquid contents of the obstructed colon. Although Nyam *et al.*[11] used decompression before anastomosis, the present authors believe that it may be more valuable to decompress the bowel early, before the mesentery is divided and the gut resected. This additional time allows improved vascularity to the collapsed bowel wall and probably permits some improvement in 'tone' and anastomotic security since the cut edges no longer appear thin walled and friable but would hold sutures almost as well as normal colon.

There is as yet no prospective randomized trial comparing decompression alone with decompression plus colonic irrigation. The only retrospective study available shows no advantage to irrigation[11]. Because lavage is cumbersome, costly, time consuming and possibly increases the risk of spillage, colonic decompression without lavage and primary anastomosis for left-sided colonic obstruction is recommended.

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Improved perineal healing after internal sphincter-preserving proctectomy in ulcerative colitis

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Presented as a poster to the Association of Coloproctology of Great Britain and Ireland, Jersey, Channel Islands, June 1998
Paper accepted 17 May 1999

Introduction

Primary perineal healing after proctectomy depends on the pathological condition prompting surgery as well as technical factors[1]. Discounting the effects of radiotherapy, persistent perineal sinuses seem to be more frequent following proctectomy for inflammatory bowel disease (IBD) than for malignancy.

One large American study[2] reported a 30-day healing rate of 61 per cent after surgery for ulcerative colitis, whereas only 80 per cent of perineal wounds had healed at 200 days after operation for IBD. A UK series[3] similarly reported primary healing in 69 per cent of patients with ulcerative colitis. The economic consequences of perineal healing failure are considerable.

Although ileal pouch–anal anastomosis is now the most frequently undertaken procedure in patients with ulcerative colitis, proctocolectomy and permanent ileostomy is still occasionally required and more certain perineal wound healing is important.

Although intersphincteric rectal excision may offer superior healing to conservative proctectomy, both techniques often result in a persistent perineal sinus (18 per cent for intersphincteric excision *versus* 33 per cent for the conservative operation)[4]. More recently, consideration has been given to a technique of partial anal conservation[5] involving stapling of the anal canal at the dentate line, despite its similarity to conservative proctectomy. A retrospective study was undertaken to determine the outcome of internal sphincter-preserving proctectomy (ISPP) in patients with ulcerative colitis.

Patients and methods

Twenty-six patients (13 women) of median age 55 (range 27–79) years who underwent ISPP for ulcerative colitis between 1986 and 1997 were analysed retrospectively. At the time of operation, 19 patients were receiving prednisolone (median dose 30 (range 5–60) mg) and one was taking adrenocorticotrophic hormone.

Five patients were lost to follow-up: three had no record of review by a surgeon and two were not reviewed by any clinician. These patients were excluded from analysis despite the assumption that wound healing had been satisfactory.

Internal sphincter-preserving proctectomy (*Fig. 1*)

Perimesenteric or perimuscular rectal excision may be employed during the abdominal phase. When the upper anal canal is approached, the low rectum is cross-clamped and the anal canal cleaned from below. The rectum is divided just above the anorectal junction (red shading) and the rectum is removed; the perineal phase is facilitated by rectal division as close as possible to the top of the anal canal.

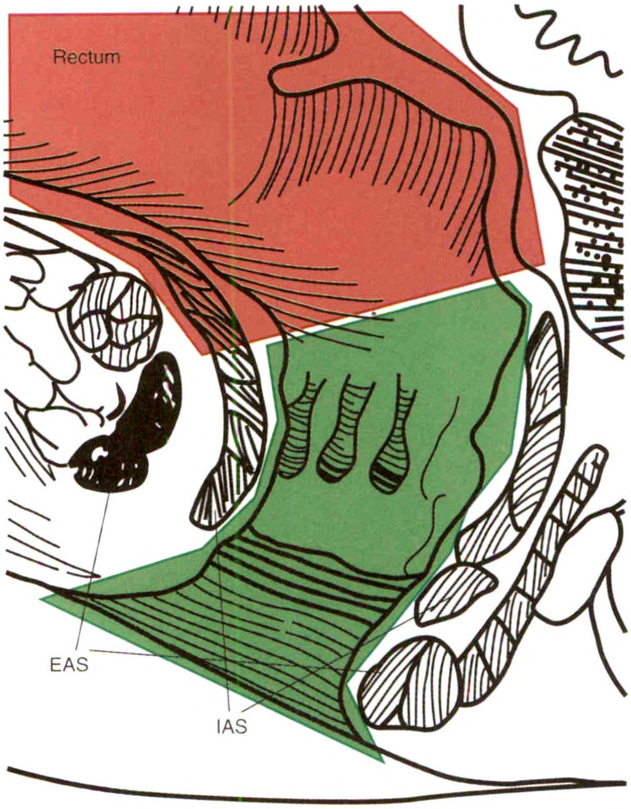

Fig. 1 The technique of internal sphincter-preserving proctectomy. The low rectum (red shading) is dissected from above. The muscular rectal wall is utilized as the plane of dissection until the upper anal canal is reached. After rectal cross-clamping, the anus and low rectal stump are cleaned from below before division below the clamp (junction of red and green shading). The anal canal and rectal stump are stripped of epithelium leaving the internal anal sphincter (IAS) (green shading). The pelvic floor is closed by approximation of the IAS with absorbable sutures, and the skin is closed primarily. EAS, external anal sphincter

The perineal operator infiltrates dilute adrenaline solution subdermally and subepithelially in the anal canal and excises all epithelium from distal to the anal verge to the point of rectal division (green shading). Sufficient perianal skin is excised to allow tension-free approximation of the perineum, avoiding a wound in a deep cleft. By this means, the natal cleft may be flattened completely.

The internal sphincter and then perineal skin are approximated with absorbable sutures and the pelvis is drained abdominally.

Results

Of the remaining 21 patients, 17 had achieved complete perineal healing at the time of first outpatient review at a median of 58 (range 14–112) days. Healing had not occurred in three patients at the first review but had done so by the next (79, 91 and 170 days). No patient required further surgical or nursing intervention. One patient remains with an asymptomatic perineal pit. Twenty of 21 patients experienced perineal healing without formation of a persistent sinus.

Discussion

Preservation of the internal anal sphincter during proctectomy for ulcerative colitis has avoided persistent perineal sinus formation. Yamamoto *et al.*[1] defined a 12-week cut-off between 'early' and 'delayed' perineal healing; by this criterion only two patients in the present series experienced delayed healing, and persistent perineal sinus was not seen. ISPP may offer improved perineal healing after proctectomy without increased technical difficulty.

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Original article

Touch imprint cytological analysis of sentinel lymph nodes for detecting axillary metastases in patients with breast cancer

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Background: Sentinel lymph node biopsy is a procedure that examines the first tumour-draining lymph node. Touch imprint cytology may provide a quick method for intraoperative screening of sentinel lymph nodes for the presence of metastases.
Methods: Touch imprint cytological analysis of sentinel lymph nodes was compared prospectively with the findings obtained on routine paraffin sections. Touch imprint slides from 55 patients with breast cancer were prepared during operation from multiple sections of sentinel lymph nodes, stained with haematoxylin and eosin. A cytopathologist blinded to the histological results interpreted the smears.
Results: The concordance between touch imprint and paraffin sections of sentinel lymph nodes was 98 per cent (54 of 55). When touch imprint analysis of sentinel lymph nodes was compared with paraffin sectioning of all lymph nodes from the axillary node dissection, the concordance was 95 per cent (52 of 55). The sensitivity and specificity of sentinel lymph node touch imprints in detecting metastases were 82 and 100 per cent respectively. The positive and negative predictive values were 100 and 93 per cent respectively.
Conclusion: Touch imprint cytology is potentially useful for the intraoperative evaluation of sentinel lymph nodes in patients with breast cancer.

Paper accepted 12 May 1999

British Journal of Surgery 1999, **86**, 1346–1348

Introduction

Axillary lymph node staging continues to be an important component of breast cancer management for planning systemic adjuvant therapy. Recently there has been considerable interest in lymphatic mapping for breast cancer to identify the first tumour-draining lymph node, termed the sentinel node. If this node is free from metastases, the remaining axillary nodes should be clear, obviating the need for a complete axillary dissection.

The status of axillary lymph nodes has been evaluated during operation by frozen section analysis, although this is not 100 per cent sensitive in comparison with paraffin section analysis. Touch imprint cytology is another method that has been evaluated during operation for several types of cancer[1,2]. Imprint cytology of axillary nodes in patients with breast cancer has the potential not only to be quicker and cheaper than routine histological examination, but also to assess a greater volume of the node by examining multiple sections, possibly resulting in improved accuracy[3–7].

The present study compared the results of touch imprint cytology of sentinel lymph nodes with paraffin section histology of the same sentinel lymph nodes and of the complete axillary specimen.

Patients and methods

Sentinel lymph nodes from patients with breast cancer, who had undergone sentinel lymph node biopsy and axillary lymph node dissection as part of their treatment between September and December 1997, were studied. Patients who had had previous breast or axillary radiation therapy, axillary surgery or chemotherapy were excluded. The sentinel lymph node biopsy technique used in this study involved injection of isosulfan blue dye (Lymphazurin; Ben Venue Laboratories, Bedford, Ohio, USA) into the breast tissue around the primary tumour or around the cavity from a previous biopsy. The first blue lymph node in the lymphatic chain was identified as the sentinel lymph node. Following excision of the sentinel node, the axillary lymph node dissection was completed for comparison[8].

Immediately after excision, the fat was dissected from the sentinel lymph nodes and each node was divided in two if the diameter was less than 8 mm, or cut into multiple sections of 3-mm thickness if the diameter was greater than 8 mm. A cellular smear was prepared by scraping one surface of each serial section with a slide and then smearing this material on to a second slide. This second slide, the touch imprint slide, was fixed immediately in 95 per cent alcohol and subsequently stained with haematoxylin and eosin. One touch imprint slide was prepared from each serial section of the sentinel lymph nodes for each patient. All slides were prepared in the operating room and stained by a surgeon. The slides were numbered consecutively and kept for examination by an experienced cytopathologist who was not aware of the histopathology results. The corresponding portion of the sentinel lymph node was labelled separately, fixed in formalin, and subjected to routine paraffin section and staining with haematoxylin and eosin. Specimens from axillary lymph node dissections were also submitted separately for routine pathological examination.

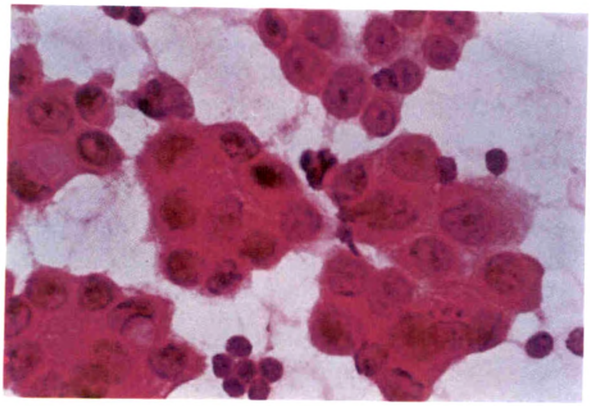

Fig. 1 This sentinel lymph node touch preparation is positive for metastatic adenocarcinoma. Note the striking difference between the large pleomorphic adenocarcinoma cells and the much smaller benign lymphoid cells (original magnification × 400)

The presence of malignant cells in the touch imprint slide was defined as a positive cytology result (*Fig. 1*). Results from sentinel lymph node touch imprint cytology were compared with those of permanent paraffin sections as the reference standard.

The Epi Info 6.0 program (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) was used for data processing. Sensitivity and specificity were calculated to determine the accuracy of the sentinel lymph node touch imprint technique.

Results

Among 60 patients who had surgery during the study period, one or more sentinel lymph nodes were identified in 55 (92 per cent). Of these 55 patients, 25 (45 per cent) presented with clinical symptoms and 30 (55%) with a mammographic abnormality. The mean(s.d.) age of the patients was 56(12·8) years. Of the 55 patients, 17 had invasive cancer, 34 had invasive and *in situ* cancer, three had *in situ* cancer and one had medullary cancer. Mean(s.d.) tumour diameter was 1·7(1·1) cm. A total of 138 sentinel lymph nodes was found (mean(s.d.) 2·5(1·9) nodes per patient), and 999 axillary lymph nodes were dissected from axillary specimens (mean(s.d.) 18(8·8) nodes per patient).

Touch imprint cytology results were 98 per cent (54 of 55) concordant with those of the paraffin sections of sentinel lymph nodes (*Table 1*). There was one false-negative finding: in one patient the touch imprint was negative but the sentinel lymph node paraffin section contained a microfocus of malignant cells (measuring approximately 1·2 × 0·3 mm). This touch preparation was less than optimal owing to limited cellularity and air-drying artefact. Imprint cytology was 93 per cent sensitive, 100 per cent specific, and had a positive predictive value of 100 per cent and a negative predictive value of 98 per cent for predicting sentinel lymph node status.

Table 1 Test characteristics of touch imprint cytological analysis of the sentinel lymph node in diagnosing metastases, using paraffin sections of sentinel and axillary lymph nodes as reference

	Paraffin section			
	Sentinel lymph node status		Axillary lymph node status*	
	Positive	Negative	Positive	Negative
Touch imprint				
Positive	14	0	14	0
Negative	1	40	3	38

*Complete axillary dissection lymph node status

Touch imprint cytology correctly predicted the status of only 52 axillary dissections in 55 patients (95 per cent accuracy; 38 true-negative and 14 true-positive patients). There were two false-negative sentinel lymph nodes from the sentinel lymph node biopsy method (*Table 1*). Imprint cytology was 82 per cent sensitive, 100 per cent specific, and had a positive predictive value of 100 per cent and a negative predictive value of 93 per cent for predicting axillary node status.

Discussion

There is considerable interest in identification of the sentinel lymph node, to minimize the complications of axillary node dissection. A sentinel node free of metastases would eliminate the need for additional node removal, whereas a sentinel node with metastases could lead to a complete dissection. A rapid and reliable means of evaluating the sentinel node at the time of operation would allow immediate decisions to be taken regarding further surgery.

Fisher *et al.*[6] reported an accuracy of only 90 per cent for frozen section of axillary nodes compared with paraffin sections, and 94 per cent for touch imprint cytology, using axillary lymph node status in the same group of patients as the reference standard. Imprint cytology may be at least as accurate as frozen section.

The sensitivity in reported series of touch imprint cytology of axillary nodes has ranged from 93 to 100 per cent[3,5–7]. The majority of these studies did not relate the results of touch imprint cytology to the lymph node status from standard axillary dissection. The sensitivity of touch imprint cytology was decreased compared with standard axillary lymph node dissection results because of limitations in the lymph node sampling method[6].

In this study touch imprint cytology was 98 per cent concordant with sentinel lymph node histological findings, but only 95 per cent concordant with axillary status, due to failure of the node sampling technique. Improvements in the sentinel lymph node biopsy technique could increase the accuracy of touch imprint cytology.

In the present study one false-negative touch imprint cytology result was in a patient with a single focus of micrometastasis. Identification and treatment of patients with micrometastatic disease may not affect survival[9,10].

Giuliano *et al.*[11] reported the use of immunohistochemical staining to increase the diagnostic sensitivity for metastases in sentinel lymph nodes. Immunohistochemical staining can also be applied to touch imprint specimens, perhaps with similar improvements in sensitivity.

Touch imprint cytology is easily performed, accurate, and also suitable for immunohistochemical staining. It could be used during operation for sentinel lymph node evaluation.

Acknowledgements

The authors thank Mr Michael Greenall, John Radcliffe Infirmary, Oxford, UK, for insight and comments that led to this study being undertaken.

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Original article

Plasma concentrations of glutathione S-transferase isoenzyme are raised in patients with intestinal ischaemia

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Background: The mortality rate associated with acute mesenteric ischaemia (AMI) remains high. Diagnosis is frequently confounded by the non-specific history and physical signs, in conjunction with the absence of a reliable biological assay. Glutathione S-transferase (GST) is an enzyme with a crucial role in cellular homoeostasis, the α isoenzyme of which is highly specific to small bowel and liver. This study assessed αGST as a marker for AMI.
Methods: Twenty-six patients with acute abdominal pain were enrolled. Each patient manifested a diagnostic dilemma, with a potential diagnosis of AMI. Plasma was reserved for αGST assay during routine blood testing and stored at −20°C for analysis. A final diagnosis was made by autopsy, laparotomy, a definitive other investigation or a return to full health.
Results: Twelve patients had AMI. Plasma αGST was significantly increased in patients with AMI ($P < 0{\cdot}0001$). Although pH differed and other biochemical changes occurred, only αGST accurately predicted AMI.
Conclusion: A threshold of 4 ng/ml for αGST was 100 per cent sensitive and 86 per cent specific for AMI. If these observations can be confirmed, evaluation of αGST may reliably predict the presence or absence of AMI.

Paper accepted 14 June 1999

British Journal of Surgery 1999, 86, 1349–1353

Introduction

Although acute mesenteric ischaemia (AMI) is a condition with an associated mortality rate that usually approximates 50 per cent[1,2], mortality rates of 33 per cent have been described when the diagnostic delay is kept to less than 12 h by using early arteriographic investigation with aggressive management[3]. Even so, the diagnosis is frequently made at too late a stage for successful intervention. This is generally attributed to the notorious difficulty of clinical diagnosis and the absence of a reliable test short of mesenteric angiography or laparotomy. Indeed, even at laparotomy, making a decision about the ultimate viability of apparently ischaemic intestine may be difficult[4,5].

The glutathione S-transferases (GSTs) are a family of enzymes involved in the detoxification of a range of toxic and foreign compounds within the cell by conjugation to glutathione. The enzymes are grouped into families based on their isoelectric point: α, π, μ and θ, as well as a microsomal form[6]. The different GSTs have relatively unique distributions in various organs[7], and this enables them to be used as relatively specific biomarkers of organ damage. Serum αGST is a more sensitive marker of hepatic injury than the aminotransferases in several conditions[8–10], while urinary αGST and πGST are specific and sensitive markers of proximal and distal renal tubular injury respectively[11,12]. αGST is also known to be present in the small intestine[13] and, based on a rodent model of superior mesenteric artery ligation, it has been suggested that it may be a sensitive marker of ischaemic injury to the small bowel[14].

This study was designed to evaluate the ability of αGST to predict intestinal ischaemia in the clinical situation. To this end, plasma concentrations of αGST were assessed in a group of patients with complex, difficult clinical presentations who complained of abdominal pain and had clinical signs potentially consistent with AMI.

Patients and methods

Twenty-six patients were selected prospectively from the cohort of patients seen during emergency call over an 18-month period. Each patient had acute abdominal pathology of unclear aetiology, and these constituted all patients seen by the authors over the time period in whom the diagnosis of AMI was considered as a diagnostic possibility. Many had undergone recent laparotomy or had significant complicated co-morbidity, including acute myocardial infarction, cardiac dysrhythmia or multiple organ failure. As a result, each patient either had a clinical diagnosis of AMI, or had no definitive diagnosis but was thought to have a significant chance of having ischaemic intestine. A final diagnosis was made either by laparotomy, autopsy, a definitive radiological investigation or a return to full health. Patients without ischaemic bowel were deemed to be controls, while those with ischaemic bowel were placed in the AMI group. All patients who underwent laparotomy and were found to have ischaemic bowel had segments of infarcted bowel that were not viable. Patients who had a diagnosis made by autopsy alone had been deemed unfit or inappropriate candidates for surgical intervention.

A separate group of patients with non-specific abdominal pain and no evidence of abdominal pathology was studied to determine the normal range of αGST.

At the time of initial clinical review, a 2·5-ml blood sample was reserved in an ethylenediamine tetra-acetic acid-coated standard phlebotomy vial. Plasma was separated and stored at – 20°C for batch analysis at a later date. Samples were also taken to determine white cell count (WCC), pH, base excess, and amylase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. These were all examined routinely using standard laboratory systems. Analysis of stored plasma samples for αGST was performed blindly in batches using the HEPKIT-Alpha (Biotrin International, Dublin, Ireland)[15]. This is a commercially available quantitative enzyme immunoassay which takes approximately 2 h. All tests for αGST were performed by persons unaware of the group to which the patients belonged.

Statistical analysis, including assessment of normal distribution of data, was performed using Sigmastat for Windows version 1.0 (Jandel Scientific Software, San Rafael, California, USA). Parametric data are presented as mean(s.d.) and were analysed using Student's *t* test. Non-parametric data are presented as median (interquartile range) and were analysed using the Mann–Whitney rank sum test. A value of $P<0{\cdot}05$ was considered to be statistically significant.

Results

Twenty-six patients with acute abdominal pathology and a complex clinical background were assessed. Twelve patients were ultimately diagnosed as having acutely ischaemic bowel (*Table 1*). Of these, six had an ischaemic segment of small bowel consistent with occlusive mesenteric ischaemia, either within 4 days of other unrelated laparotomies ($n=3$), after coronary artery bypass surgery ($n=1$) or without an obvious predisposing cause ($n=2$). The other six patients had generalized mesenteric ischaemia consistent with a hypoperfusional non-occlusive injury secondary to myocardial failure ($n=4$) or related to multiple organ failure with hypotension ($n=2$). The remaining 14 patients were designated as controls and had a final diagnosis of intra-abdominal sepsis ($n=5$), pancreatitis ($n=2$), intestinal obstruction ($n=2$) or myocardial infarction ($n=1$). Mesenteric ischaemia was assumed to be absent in four patients whose condition resolved completely.

Plasma α glutathione levels

Measurement of αGST levels in control patients revealed values of less than 3 ng/ml in all except two patients, with a median level of 1·6 ng/ml. One control patient (αGST 11·0 ng/ml) had normoamylasaemic pancreatitis confirmed radiologically, while a second (αGST 29·9 ng/ml) had end-stage septicaemic shock secondary to a perforated peptic ulcer. All patients with mesenteric ischaemia had an αGST level greater than 5 ng/ml. The median value was significantly raised at 75·8 (range 5·2–400) ng/ml ($P<0{\cdot}0001$). A

Table 1 Results of haematological and biochemical assessment of patients with abdominal pain of unclear aetiology and a possible diagnosis of ischaemic bowel

Diagnosis	αGST (ng/ml)*	pH*	Base excess (mmol/l)†	Amylase (units/dl)*	WCC (× 10⁹ per l)†	AST (units/l)*	ALT (units/l)*
Normal range	—	7·35–7·45	–2·0 to +2·0	80–330	4–11	5–40	5–40
AMI ($n=12$)	75·8 (22·4–153·0)	7·18 (7·10–7·40)	–9·0(6·3)	275 (155–344)	17·5(7·6)	165 (33–305)	69 (30–288)
Patients per assay	12	10	10	12	11	11	11
Control ($n=14$)	1·6 (0·8–2·2)	7·40 (7·39–7·40)	–3·4(6·5)	208 (74–535)	12·5(8·8)	38 (30–97)	26 (17–92)
Patients per assay	14	6	6	8	12	10	10
P	<0·0001‡	0·212‡	0·14§	0·64‡	0·17§	0·06‡	0·08‡

*Values are median (interquartile range) or †mean(s.d.). GST, glutathione S-transferase; WCC, white cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AMI, acute mesenteric ischaemia. ‡Mann–Whitney rank sum test, §Student's *t* test

scattergram of the αGST values for control and AMI groups demonstrated a line of demarcation between groups, suggesting the upper limit of normal to be approximately 3 ng/ml (*Fig. 1*). The normal range for the assay (95 per cent confidence interval) calculated from the patients with non-specific abdominal pain was 0–2·8 ng/ml. Assessment of αGST proved to be highly accurate at predicting AMI with an overall predictive value of 92 per cent using a cut-off value of 4 ng/ml (*Table 2*).

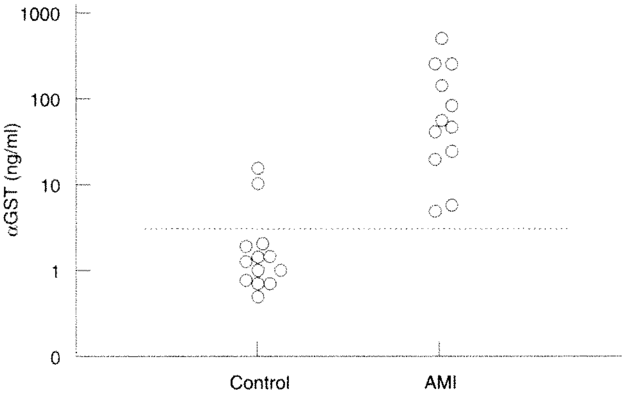

Fig. 1 Dot plot demonstrating the range of α glutathione transferase (GST) values in patients with acute mesenteric ischaemia (AMI) and without mesenteric ischaemia (control). A value of 4 ng/ml (dotted line) was selected as the upper limit of normal for αGST

Other biochemical parameters (*Tables 1 and 2*)

Although patients with AMI had a lower pH than controls, the overall accuracy was only 69 per cent. Base excess was reduced in patients with AMI, but the low specificity of this test led to an accuracy of only 67 per cent. Similarly, amylase level and WCC were increased in patients with AMI, but predictive values were poor. Serum transaminase (AST and ALT) levels were increased in several patients with AMI; however, this tended to be associated with hypoperfusional non-occlusive ischaemia and predictive values for AMI were low.

Subgroup analysis of patients with acute mesenteric ischaemia (*Table 3*)

Inspection of αGST values for patients with AMI suggested that these patients might be divided into two groups. The six patients who had an ischaemic segment of small bowel

Table 2 Predictive values and accuracy of α glutathione S-transferase isoenzyme analysis at detecting the presence of mesenteric ischaemia in patients with abdominal pain of unclear aetiology in comparison to other standard available measurements, using a cut-off value of 4 ng/ml

	αGST (ng/ml)	pH	Base excess (mmol/l)	Amylase (units/dl)	WCC ($\times 10^9$ per l)	AST (units/l)	ALT (units/l)
Normal range	0–4	7·35–7·45	−2·0 to +2·0	80–330	4–11	5–40	5–40
Sensitivity	100	60	80	25	82	70	73
Specificity	86	83	40	63	58	50	60
PPV	86	86	73	50	64	58	67
NPV	100	56	50	36	78	63	67
Accuracy	92	69	67	40	70	60	67

Final diagnosis was determined by laparotomy, autopsy, a definitive investigation or return to full health. A test was considered positive when outside the normal range in any patient with acute mesenteric ischaemia. GST, glutathione S-transferase; WCC, white cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PPV, positive predictive value; NPV, negative predictive value

Table 3 Comparison of diagnosis, α glutathione S-transferase, aspartate aminotransferase and alanine aminotransferase levels for patients with mesenteric ischaemia with an ischaemic segment of bowel ($n = 6$) or a generalized non-occlusive mesenteric ischaemia ($n = 6$)

Diagnosis	αGST (ng/ml)*	AST (units/ml)†	ALT (units/ml)†
Segmental ischaemia	38·1(40·3)	62 (29–108)	35 (21–62)
Global (non-occlusive) ischaemia	176·2(23·6)	1210 (234–3527)	292 (224–1100)
P	0·026‡	0·038§	0·009§

Values are *mean(s.d.) or †median (interquartile range). GST, glutathione S-transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase. ‡Student's *t* test; §Mann–Whitney rank sum test had significantly lower levels of αGST, AST and ALT than the six who had hypoperfusional non-occlusive disease, suggesting a more global pattern of ischaemia with associated hepatic hypoperfusional injury in the latter group.

Discussion

Of the 12 patients described in this study who had mesenteric ischaemia, only six had traditional AMI with a simple defined segment of ischaemic bowel. Many patients had coexisting pathologies which complicated the clinical presentation, and led to dual diagnoses such as AMI with multiple organ failure and hypoperfusion. Even so, αGST accurately detected ischaemic bowel of any type in all affected patients with a high degree of accuracy.

Many tests have been used previously in an attempt to diagnose AMI accurately. Serum markers have been evaluated extensively, but most of those studied to date, including leucocyte count, pH, base excess, isoenzymes of creatine kinase, and AST, have not been sufficiently accurate to pass into clinical practice[16]. More recently, studies using models of superior mesenteric artery ischaemia have suggested that intestinal fatty acid binding protein or serum D(–)-lactate may be a useful marker of mesenteric ischaemia[17,18]. Indeed, the latter test may be of some use in the clinical arena as the serum D(–)-lactate level appears to be significantly raised in patients with AMI, although it is also increased in patients with intestinal obstruction and other forms of abdominal catastrophe[19]. More recently serum D(–)-lactate has been used to help predict colonic ischaemia after ruptured abdominal aortic aneurysm repair, with a sensitivity of 82 per cent and a specificity of 77 per cent[20]. Similarly, the intestinal fatty acid binding protein level was shown to be raised in all of five patients with mesenteric infarction, although it was only increased in two of eight patients with strangulated necrotic bowel which required resection[21]. None of these serum-derived tests has as yet entered routine clinical practice. Angiography and laparotomy remain the most tested and accurate means of diagnosis, but unfortunately the diagnosis is frequently confirmed at autopsy.

In the present study, an αGST level of less than 4 ng/ml appeared to exclude the possibility of ischaemic bowel with a negative predictive value of 100 per cent. This may be the most important conclusion of the study, as it suggests that AMI may be excluded from a differential diagnosis in the presence of a normal αGST value. As the test is commercially available and can be completed with routine laboratory equipment in approximately 2 h, it could be used in the clinical assessment of patients who have abdominal pain and a significant possibility of AMI. At present, the assay should be used with caution in a population with a markedly lower incidence of AMI, as the positive predictive value would fall in accordance with incidence (24 per cent PPV at 5 per cent incidence; although NPV unchanged at 100 per cent).

A raised level of αGST strongly suggests the presence of AMI, with an overall accuracy of 92 per cent in patients suspected of having AMI. In patients with abdominal pain who are not in a hypoperfusional state this is highly suggestive of the presence of a segment of ischaemic bowel. In the context of the patient in intensive care, who may be hypotensive and in multiple organ failure, and who has a markedly raised αGST level with a concomitant abnormality in AST and ALT, it must be considered that non-occlusive global hypoperfusion is also contributing to a degree of hepatic ischaemia.

It remains to be seen whether αGST can diagnose ischaemic bowel before the onset of infarction in the clinical situation. Clearly the assay has potential in assessment of the complex acute abdomen, particularly by allowing the clinician to reliably exclude the presence of AMI when the αGST concentration is less than 4 ng/ml. This novel, reproducible assay appears useful in the clinical situation and warrants further investigation.

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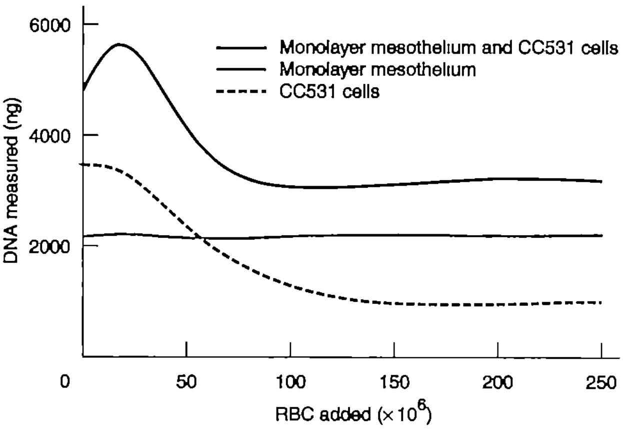
Erratum

M. E. E. van Rossen, M. P. O. Stoop, L. J. Hofland, P. M. van Koetsveld, F. Bonthuis, J. Jeekel, R. L. Marquet and C. H. J. van Eijck. Red blood cells inhibit tumour cell adhesion to the peritoneum. *Br J Surg* 1999; **86:** 509–13.

The correct version of *Fig. 1* is as follows:



The Journal apologizes for this error.

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Treatment of gallbladder cancer by radical resection

Sir

We read the article by Todoroki *et al.* (*Br J Surg* 1999; **86**: 622–7) with interest since they report the 5-year survival rate for T_1 gallbladder carcinomas as 100 per cent with a simple cholecystectomy. The tumour node metastasis classification of stage T_1 can be subdivided into T_{1a} and T_{1b} when there is invasion of the mucosa and penetration through the mucosa into the muscle layer (but not reaching the perimuscular connective tissue of the gallbladder) respectively. Results reported by the French Surgical Association Survey[1] looking at 724 patients revealed a 28 per cent 5-year survival rate (in patients with tumour equivalent to T_{1b}). Hence, this is a much more advanced condition with a poor prognosis. We agree that a simple cholecystectomy is enough for patients with T_{1a} disease but, because of the poor prognosis of T_{1b}, we believe that an extended cholecystectomy is required[2].

The vast majority of early T_{1a} and T_{1b} gallbladder carcinomas are removed laparoscopically with subsequent development of port-site metastases and peritoneal deposits. We suggest that all suspicious gallbladders[3] (thickened, chronically inflamed, dense adhesions, a long history and whether the patient has taken the oral contraceptive pill and is a smoker) should be opened, inspected and sent for frozen-section analysis. The procedure should be an open one if the frozen-section analysis reports T_{1b} early gallbladder carcinoma. An extended cholecystectomy with excision of the port sites and cytostatic washing of the abdomen should be carried out[4].

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Author's reply

Sir

We appreciate the interest in our paper. Based on our results and those of others[1], we believe that patients with either T_{1a} or T_{1b} tumours would have no lymph node involvement and, therefore, a simple cholecystectomy should suffice. Lymphadenectomy also provides tissue for overall disease staging. If there is a suspicious lesion located on the cystic duct or on the neck of the gallbladder we usually consider open surgery to remove the primary lesion together with regional lymph nodes. If frozen-section analysis reveals malignancy then hilar bile duct resection and regional lymph node dissection are carried out. The French Surgical Association Survey[2] reported a very poor prognosis for patients with T_1 disease but this study was conducted by questionnaire from 73 different institutions. Patients with understaged disease may have been included because of the lack of lymph nodes. Some patients with T_{1b} disease might have lymph node involvement and might actually have locally advanced disease. Shimada *et al.*[1] reported a 100 per cent 5-year survival rate for patients with T_1 disease (T_{1a}, n=4; T_{1b}, n=3) and those seven patients had no lymph node involvement as in our patients (T_{1a}, n=8, T_{1b}, n=5). This is too small a sample size to draw any conclusion concerning the adequacy of treatment. We, therefore, perform laparoscopic cholecystectomy in patients with a possible T_1 tumour, especially if there is no elevation of tumour markers such as CA19-9 or carcinoembryonic antigen. When there is apparent elevation of those markers, however, we conduct open surgery. For patients with polypoid tumours larger than 10 mm in diameter, we evaluate tumour blood flow by ultrasonography to evaluate the possibility of malignancy and decide whether open or laparoscopic surgery should be carried out.

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Clinical significance of telomerase activity in the non-cancerous epithelial region of oesophageal squamous cell carcinoma

Sir

We read with interest the article by Koyanagi *et al.* (*Br J Surg* 1999; **86**: 674–9). The authors observed lymphovascular invasion in three of 45 specimens that were telomerase-negative and from adjacent non-cancerous tissues. Careful analysis of *Table 1* reveals that 26 corresponding carcinomas were associated with nodal metastasis. This may imply a high false-negative rate for telomerase detection in the adjacent non-cancerous tissue. The authors do not seem to have used an internal telomerase assay standard to detect false-negative results due to the presence of Taq DNA polymerase inhibitors despite using an RNase to confirm that the DNA ladder generated by polymerase chain reaction and electrophoresis was specifically due to telomerase. We also believe that telomerase results from endoscopic biopsy specimens should be interpreted with caution as 10 000 blood cells are sufficient to give a positive telomerase result. The authors' hypothesis can be alternatively tested by measuring human telomerase reverse transcriptase (hTRT) mRNA expression in the adjacent tissue. The newly described hTRT gene codes for the catalytic subunit of telomerase and has been found to correlate with telomerase activity and the cellular origin of the enzyme[1].

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Authors' reply

Sir

We thank Mr Mokbel and colleagues for their interest in our article. Regarding the invasion of blood or lymphatic vessels, the mechanism of lymphovascular flow at the oesophageal wall is uncertain. It has been considered that the lymphatic capillary plexus of the mucosal and submucosal layer communicates with widely-spaced channels in the muscular and adventitial layers and these channels directly communicate with para-oesophageal nodes[1]. As described previously, the ratio of intramural metastasis that was caused by infiltrating cancer cells via the transmural lymphatic pathway was less than that of regional lymph node metastasis in clinical data[2,3]. The low rate of telomerase activity in the adjacent non-cancerous tissues implied less incidence of intramural metastases, not a high false-negative rate in non-cancerous tissues.

We have the results of marker ladder and positive and negative controls (RNase treatment), but as the assay method and significance are regarded as definitely established, we removed these results from our paper according to the reviewer's comment. Our methods were not quantitative, but showed that positive or negative telomerase activity clearly gave useful results. We believe that quantitative methods are not always more useful than our methods.

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Colonic motility is abnormal before surgery for rectal prolapse

Sir

We are told in the results section of this paper by Brown *et al.* (*Br J Surg* 1999; **86**: 263-6) that marker studies performed in the patient group were normal in five of the seven patients. As colonic content moves from one segment to another by way of colonic mass contractions, these five patients should have had recordable peristaltic waves. A more reasonable explanation for their absence is that the motility catheter was not placed sufficiently proximal. The tip of the catheter was located in the ascending colon in all controls[1] but in only one patient with rectal prolapse (incidentally the one with colonic mass actions present). As mass actions originate in the right colon and progress for a variable distance, it is reasonable to suggest that in all but one case the catheter was not proximal enough to record them.

Recordings of the gastrocolic reflex have been made in the sigmoid colon and as this reflex is in part mediated through the vagus nerve it would have been more appropriate to make this recording in the transverse colon. The failure to present data for the transverse colon poses the question of how many perfusion points were present in this segment of the colon.

Instead of postulating a new pathophysiology for rectal prolapse it would be more appropriate to expand the amount of control data (as advised by this author[1]) and reflect objectively on possible shortcomings of this study.

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1 Macdonald A. Aspects of colonic motility in idiopathic slow transit constipation. MD Thesis, University of Glasgow, 1996.

Authors' reply

Sir

Many of the points raised by Mr MacDonald were acknowledged in our paper and, in particular, we gave details of the exact position of the colonic catheter and declared the difficulties involved in using this technique. Indeed, by presenting all the data, we enabled readers to draw their own conclusions.

In clinical practice it is not uncommon for the results of colonic motility investigations to be apparently contradictory, presumably because the investigative methods are not truly physiological. Clearly it would have been better if all the catheters had been in the ascending colon. There is considerable debate about the site of origin of high-amplitude propagated colonic contractions (HAPCs). Some state that HAPCs commence in the caecum and ascending colon[1], while others believe that the transverse colon is the site of origin[2–4] but consider that the high amplitude wave is propagated as far as the lower descending or sigmoid colon.

We have assessed the colonic response to a meal by comparing left colonic motility in patients and controls. Like other authors[2–4] we have referred to this as the gastrocolic reflex, though this term may be less than ideal. We consider our conclusions to be measured and reasonable on the basis of the data.

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Pancreatic Disease - Towards the Year 2000. 2nd ed.

C. D. Johnson and C. W. Imrie (eds)

240 × 158 mm Pp 468 Illustrated 1999 Heidelberg. Springer. £80

Searching www.amazon.com and Barnes and Noble (www.bn.com) internet sites (keyword 'pancreas') I found 168 and 92 books respectively. So what is new here? This book is a collection of 40 well written and edited short chapters aimed at providing 'all you wanted to know about pancreatic disease', or almost all. There are five sections: acute pancreatitis, transplantation, chronic pancreatitis, endocrine-exocrine interactions and cancer. The anglo-teutonic co-operation in this book is impressive, with 38 of the authors from the UK and 19 from Germany. The franco-americano phobia is, however, disappointing (three French and one American). An immense spectrum is covered, from pure basic science to absolute surgery. Chapters are exhaustively and freshly referenced. Typically, such a book is prone to duplications and the quality of chapters is not uniform. I agree with the editors that this volume represents a 'true reflection of our current knowledge'; I am surprised, however, that a topic such as pseudocyst is mentioned only sporadically, to discuss its magnetic resonance diagnosis and endoscopic treatment. The editors of BJS asked me to consider whether this book 'fills a gap in the market' but cautioned against empty phrases such as 'should have a place in any library'. Well, it is very hard today to find a 'gap' and the existing gaps become narrower each day. This is, however, a very readable and informative 'small book' which should greatly appeal to anyone treating, learning about, or writing or operating on pancreatic diseases. It has a place in any departmental library (sorry) and is a potential source of pleasure to individual buyers.

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Ischaemia-Reperfusion Injury

P. A. Grace and R. T. Mathie (eds)

251 × 190 mm Pp 384. Illustrated 1999 Oxford: Blackwell Science. Price not supplied

This is an excellent treatise on ischaemia-reperfusion injury that looks at a whole range of issues. Despite having a multiauthorship, it is extremely well laid-out and comprehensive, with a gratifyingly small amount of overlap between the chapters. This is a tribute to the editors. One is counselled in reviewing these books, not to use the cliche 'this is a book that should be on every surgeon's shelf' but, in this case, I would almost make an exception. Modern surgery and the management of vascular and other surgical patients dictate that a fundamental understanding of the pathophysiology of ischaemia, and the effects of reperfusion, are clearly understood. Although this is an ever-developing field, this book clearly sets out our current understanding of this complex area. It is extremely well referenced and all chapters are written by acknowledged experts in their field.

This text will be useful to anyone who is involved in basic vascular research. It will, however, appeal also to a wider audience; many of the chapters will be of enormous interest to the less academically minded surgeon. The scope of the book is such that it will be informative to virtually all the subspecialties in surgery, not just vascular. It is, necessarily, very detailed and the average surgeon will undoubtedly read it selectively. This is aided by the structure of the chapters, most of which can be read easily on their own, without the necessity to have read the previous chapters. Most of the chapters are well illustrated and the authors should be congratulated on achieving a reasonable consistency of style. Overall, this is a superb book and one that I will personally refer to often.

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Advanced Precautions for Today's O.R. The Operating Room Professional's Handbook for the Prevention of Sharps Injuries and Bloodborne Exposures

M. S. Davis

228 × 153 mm Pp. 158 Not illustrated 1999 Atlanta, Georgia Sweinbinder Publications $14 95.

This short book highlights some of the hazards faced by both the surgical team and patients on entering the operating theatre. It specifically addresses the problems of potential exposure to viral blood-borne pathogens. Its first section provides an overview of the problem, and subsequent sections detail how solutions may be identified and how any necessary changes can be implemented to provide a safer environment. The author is a practising clinician and the style of the book is both personal and informal. Indeed the initial stimulus for writing the book came from a bad personal experience within the operating theatre. The author's enthusiasm for his subject comes through very strongly in the text and his arguments are presented in a clear and persuasive fashion. Overall, the book is a clear, informative and practical guide to relatively simple measures that may be taken to make the operating theatre a safer workplace for all members of the surgical team and their patients. There should be a place for this volume in the coffee rooms of operating suites throughout the country.

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Scientific Surgery

Klomp HM, Geert H, Spincemaille HJJ, Steyerberg EW, Habbema JDF, van Urk H for the ESES Study Group. Spinal cord stimulation in critical limb ischaemia: a randomised trial. *Lancet* 1999; **353**: 1040-4.

Some 120 patients unsuitable for vascular reconstruction were randomly allocated to cord stimulation or best medical therapy After 2 years, survival (67 *versus* 65 per cent respectively) and amputation rates (25 *versus* 29 per cent) were similar, but analgesic requirements were reduced by cord stimulation

Heikkinen T-J, Haukipuro K, Korvukangas P, Sorasto A, Autio R, Sodervik H *et al.* Comparison of costs between laparoscopic and open Nissen fundoplication: a prospective randomised study with three month follow-up. *J Am Coll Surg* 1999; **188**: 368-76.

Forty-two patients were included. Both operations were equally safe and effective Hospital costs were similar, but speedier convalescence after laparoscopic surgery resulted in significantly lower total costs

Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg* 1999; **229**: 467-77.

Eleven trials including over 1000 patients were included Nutritional support significantly reduced the rate of infective complications and duration of hospital stay but had no effect on mortality

Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O *et al.* Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase III trial. *Arch Surg* 1999, **134**: 428-33.

In a study of 206 patients, addition of arginine, RNA and omega 3 fatty acids to routine enteral feeding significantly reduced the rate of sepsis (14 *versus* 30 per cent, $P = 0{\cdot}009$) and duration of hospital stay (11·1 *versus* 12·9 days, $P = 0{\cdot}01$).

Kester RC, Antrum R, Thornton CA, Ramsden CH, Harding I. A comparison of teicoplanin *versus* cephradine plus metronidazole in the prophylaxis of postoperative infection in vascular surgery. *J Hosp Inf* 1999; **41**: 233-44.

Some 272 patients were randomized to a single dose of teicoplanin or three doses of the combined regimen There was no significant difference in the subsequent wound infection rate (4·4 *versus* 5·9 per cent respectively)

Belghiti J, Noun R, Malafosse R, Jagot P, Sauvanet A, Pierangeli F *et al.* Continuous *versus* intermittent portal triad clamping for liver resection: a controlled study. *Ann Surg* 1999; **229**: 369-75.

Intermittent clamping caused a greater rise in liver enzymes in this study of 86 operations, though intraoperative blood loss was significantly more Continuous clamping was particularly hazardous in patients with abnormal liver function before operation

Martino K, Merrit S, Boyakye K, Sernas T, Koller C, Hauser CJ *et al.* Prospective randomized trial of thoracostomy removal algorithms. *J Trauma* 1999; **46**: 369-73.

A total of 205 patients with a chest drain following trauma were studied The drains were either simply removed or withdrawn after a period of low wall suction through a water seal The latter method allowed a few occult leaks to be detected and reduced the rate of repeat chest drainage

Law W-L, Chu K-W. Triple rubber band ligation for hemorrhoids: prospective randomized trial of use of local anesthetic injection. *Dis Colon Rectum* 1999; **42**. 363-6.

Injection of local anaesthetic into the banded tissue did not reduce the rate of significant pain (26 *versus* 20 per cent no local anaesthetic) or tenesmus (32 *versus* 41 per cent) in this study of 101 patients

Dziri C, Paquet J-C, Hay J-M, Fingerhut A, Msika S, Zeitoun GS *et al.* Omentoplasty in the prevention of deep abdominal complications after surgery for hydatid disease of the liver. a multi-center prospective randomised trial. *J Am Coll Surg* 1999; **188**: 281-9.

Some 115 patients were randomized Omentoplasty reduced the rate of deep abdominal complications (10 *versus* 23 per cent, $P < 0{\cdot}05$) and deep abscesses (nil *versus* 11 per cent, $P < 0{\cdot}03$) The duration of hospital stay was similar

Dorval T, Negrier S, Chevreau C, Avril M-F, Baume D, Cupissol D *et al.* Randomized trial of treatment with cisplatin and interleukin-2 either alone or in combination with interferon alpha-2a in patients with metastatic melanoma. *Cancer* 1999; **85**: 1060-6.

The study included 117 patients, the addition of interferon did not improve the median survival (10·4 months no interferon *versus* 10·9 months)

Blajman C, Balbiani L, Block J, Coppola F, Chacon R, Fein L *et al.* A prospective randomized Phase III trial comparing combination chemotherapy with cyclophosphamide, doxorubicin and 5-fluorouracil with vinorelbine plus doxorubicin in the treatment of advanced breast cancer. *Cancer* 1999; **85**: 1091-7.

Some 170 patients were treated The two regimens were similar in effect and toxicity The median survival was 17·3 months for the two-drug, and 17·8 months for the three-drug regimen

Fitridge RA, Dunlop C, Raptis S, Thompson MM, Leppard P, Quigley F. A prospective randomised trial evaluating the haemodynamic role of incompetent calf perforating veins. *Aust N Z J Surg* 1999; **69**: 214-6.

Thirty-eight legs having surgery for uncomplicated varicose veins with perforator incompetence were randomized to perforator ligation or control. The results of plethysmography 3 months later were similar in the two groups

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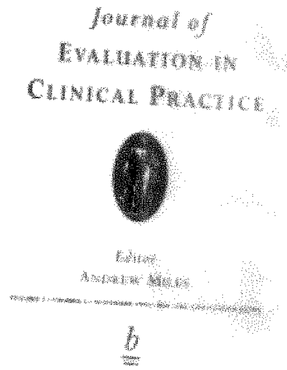

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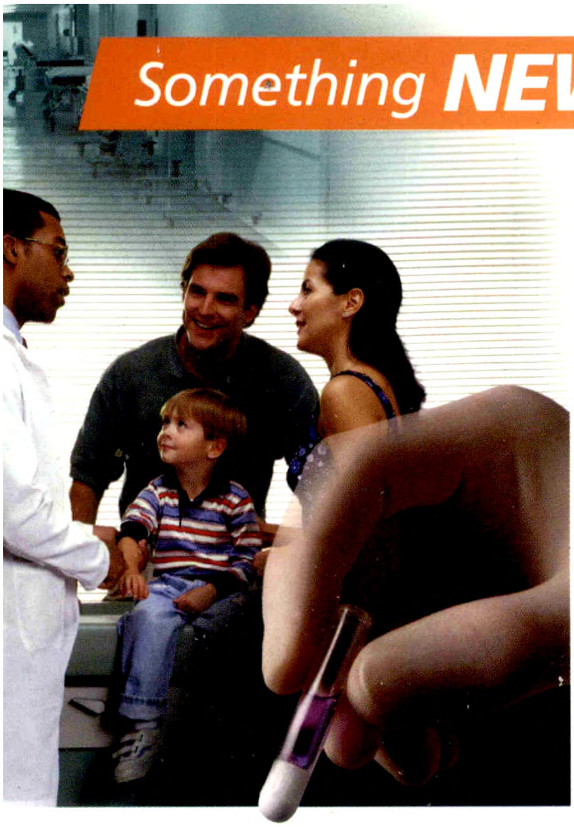

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The *British Journal of Surgery* ISSN 0007-1323

Published on behalf of the British Journal of Surgery Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
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*Periodicals postage is paid at Rahway, NJ and Additional Mailing offices. Postmaster: send address corrections to. the *British Journal of Surgery*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

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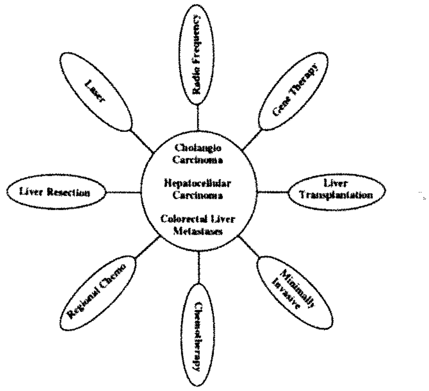

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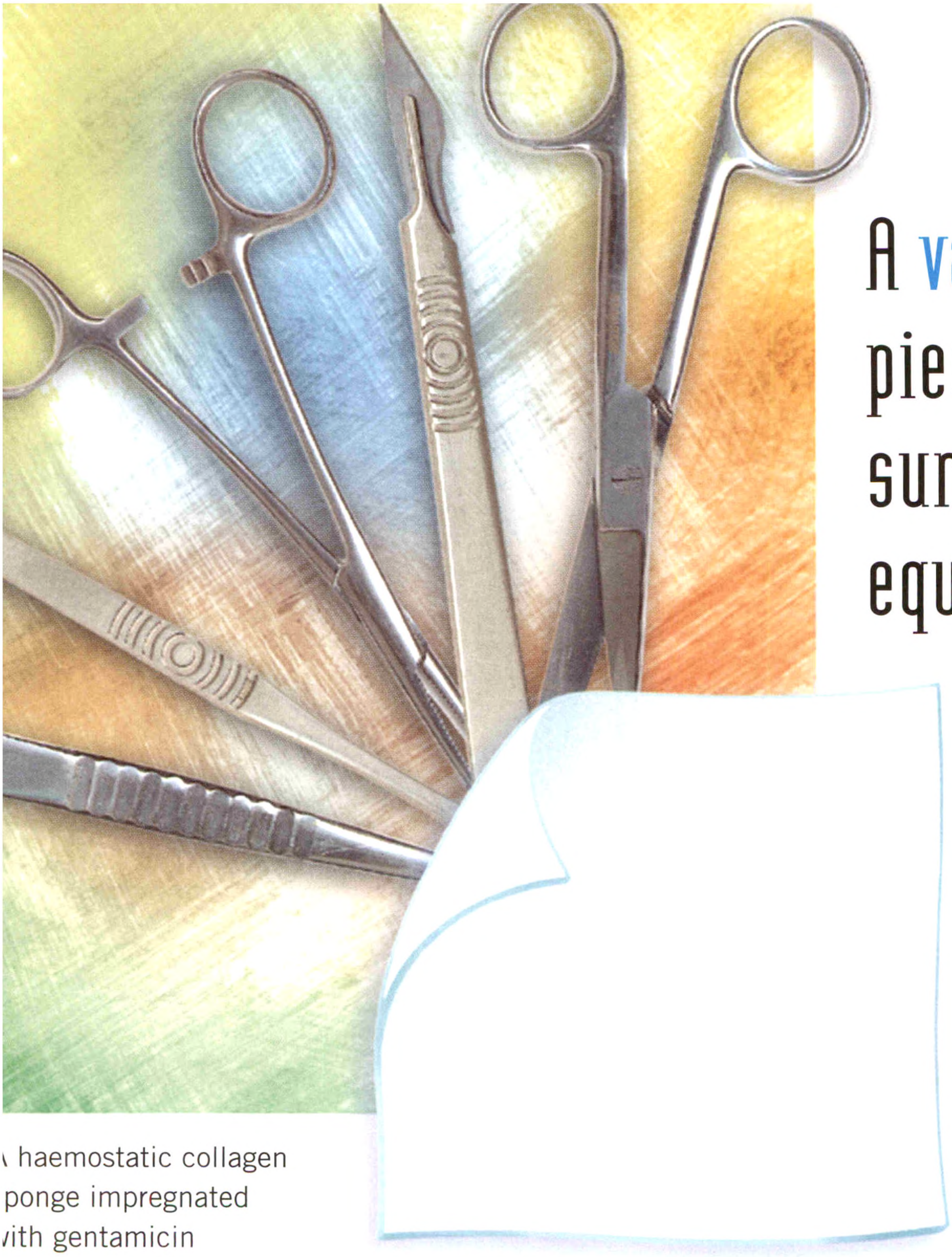

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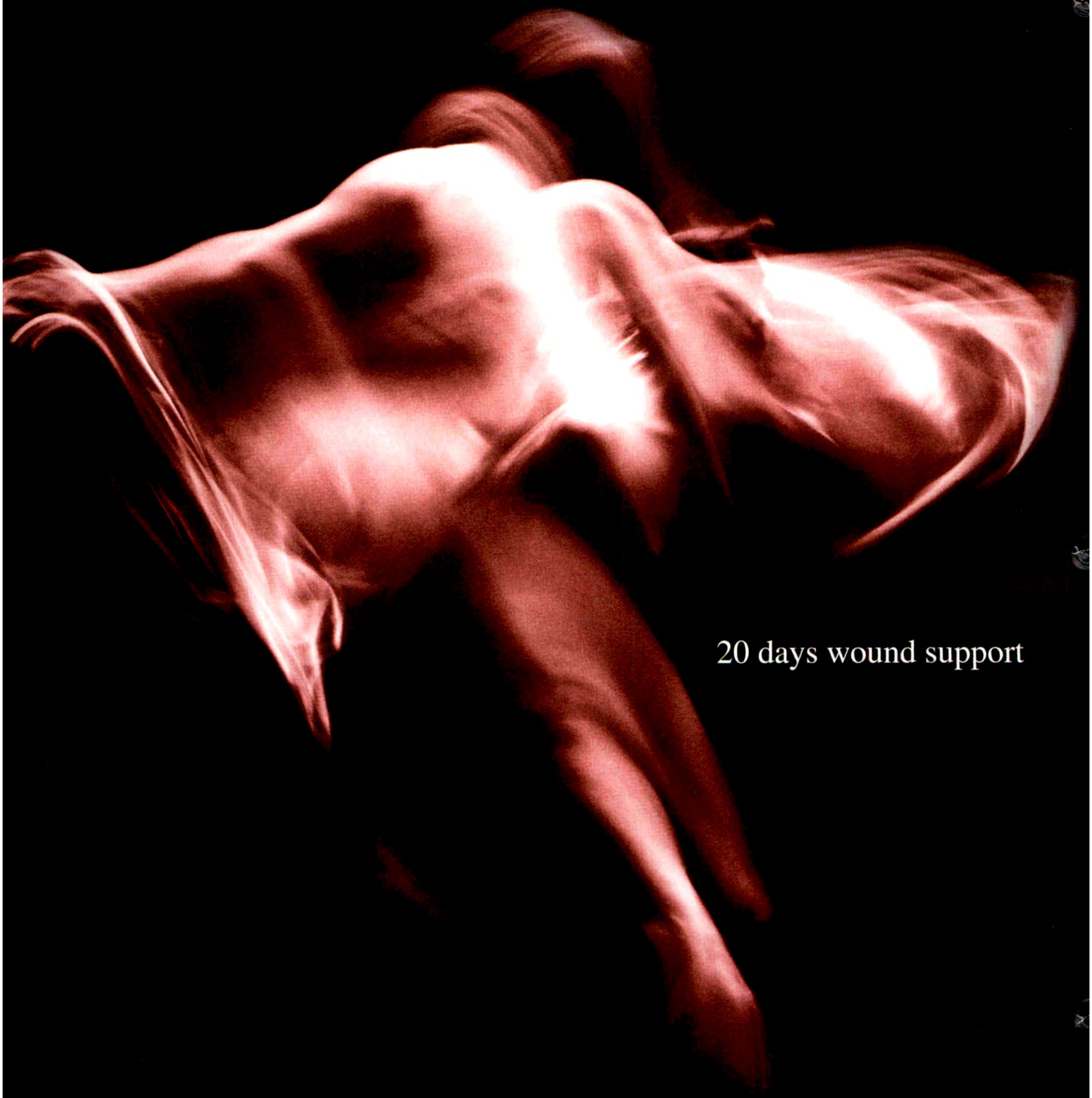

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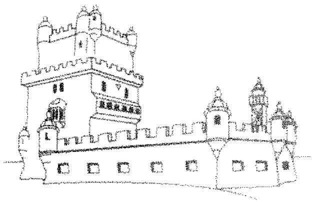

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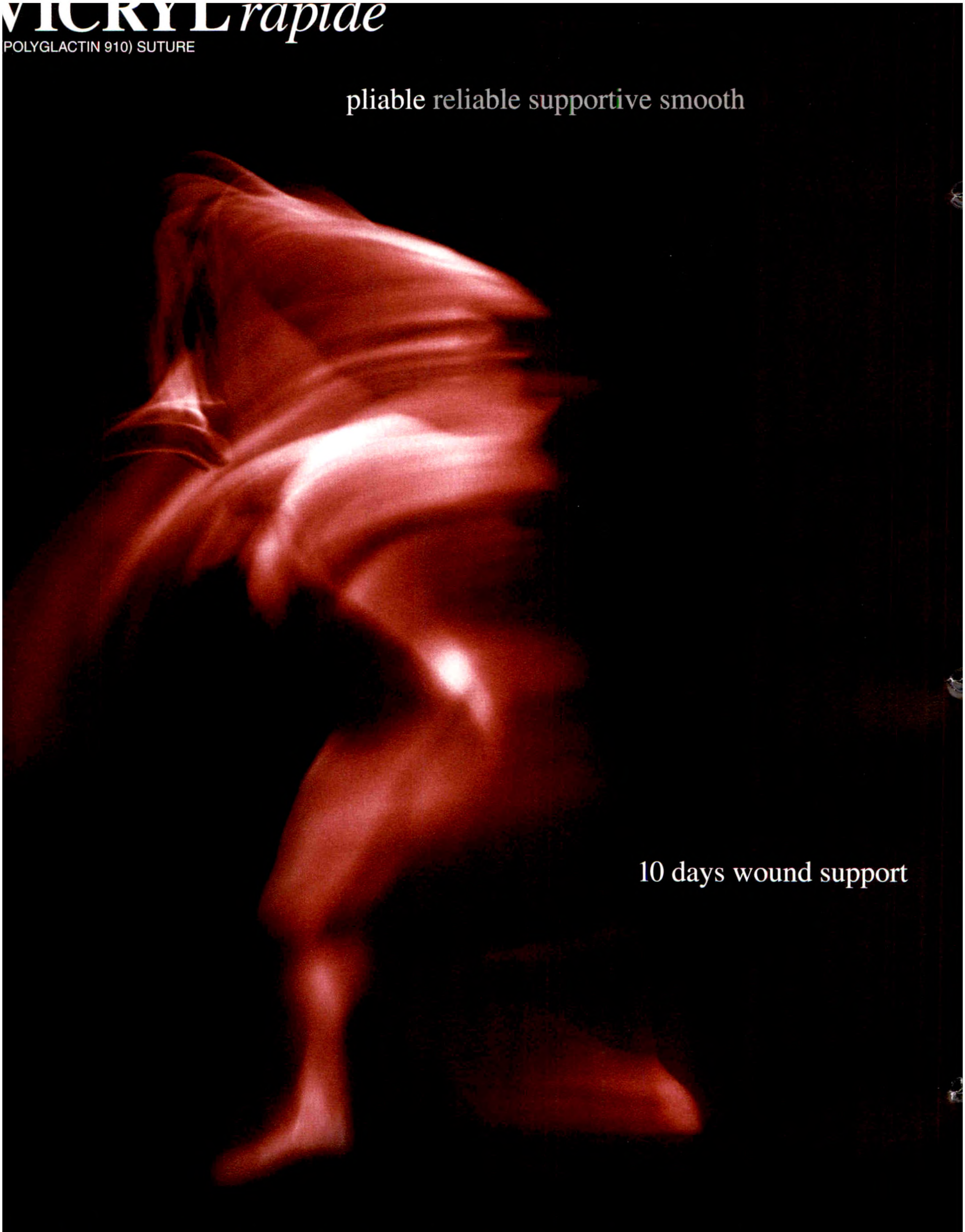

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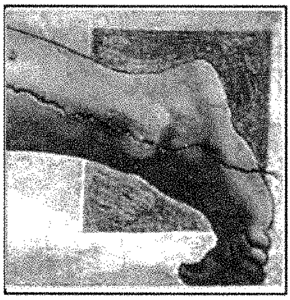

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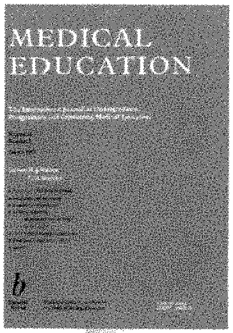

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Leading article

Centralization of surgery for periampullary malignancy

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Resection of periampullary carcinoma has traditionally been associated with a high morbidity rate (40–60 per cent) and a mortality rate of around 20–30 per cent. The dismal prognosis, even after resection, has led to a nihilistic approach by some physicians; Gudjonsson[1] concluded in his extensive review of 80 000 patients with pancreatic carcinoma, with an overall 5-year survival rate of 0·4 per cent, that 'pancreatic resections are wasteful of resources'. However, recently the mortality rate has decreased dramatically to less than 5 per cent and several series of over 100 consecutive resections without a death have now been reported, leading to a more optimistic view in favour of resection.

Parallel to these data, from centres with a special interest in pancreatic surgery, come a number of reports that highlight the influence of hospital volume on hospital mortality rates and/or patient outcome[2–8]. Whereas an earlier study showed a correlation mainly between hospital volume and postoperative complications[2], more recent studies from two regions in the USA described a significantly lower hospital mortality rate in high-volume institutions compared with that in low-volume institutions (respectively 2·2 *versus* 19 per cent, and 5·5 *versus* 18·9 per cent)[3,4]. Furthermore, in a UK survey, specialist pancreatic units had results (mortality rate 5·9 per cent) that were superior to those from non-specialists units[5]. Centralization of pancreatic surgery is not routine in most countries. A nationwide study from the Netherlands in 1994–1995 reported that 46 per cent of pancreatoduodenectomies were performed in small-volume centres (doing fewer than five resections per year). The hospital mortality rate was 15·9 per cent, compared with 1·5 per cent in high-volume centres (more than 25 resections per year)[6]. In a second follow-up study conducted in 1996–1997 there was no sign of centralization (44 per cent were low-volume centres) and the mortality rate had not changed (15·0 *versus* 1·2 per cent). One might argue, however, about the scientific standard of the above-mentioned studies. Most were retrospective, used state discharge databases without correction for case mix, and hospital mortality was generally the endpoint. These reports might also have an additional bias, because the authors came from the high-volume (i.e. low mortality rate) hospitals[4–6].

Long-term survival and local recurrence rates are generally accepted as the best endpoints after operation for cancer. Local recurrence clearly reflects the quality of the surgical technique and its performance for low-risk surgery, such as breast and colorectal operations. Pancreatic surgery, however, may be associated with a high mortality rate and a variation of 10 per cent in hospital mortality rate significantly affects the overall outcome, in particular when the adjuvant therapies currently available have only limited impact on the absolute 5-year survival rate. In such circumstances hospital mortality could be accepted as a reasonable endpoint for assessing outcome of resection.

The potential bias involved in using state discharge databases to analyse mortality relates to the problem of case mix. It has been suggested that surgeons in low-volume hospitals treat more high-risk patients, with more co-morbidity and more advanced disease; this would influence the outcome negatively. The studies detailed above did not evaluate or correct for these factors[3–6]. In recent work, using a population-based database of individuals aged over 65 years, which evaluated the 30-day mortality rate, the same impact of hospital volume on mortality rate was found not only for pancreatic resection ($P = 0{\cdot}004$) but also for other high-risk surgery, such as oesophagectomy ($P < 0{\cdot}001$) and liver resection ($P = 0{\cdot}04$)[7]. No difference in co-morbidity, stage of disease, and age for high- and low-volume hospitals was found in that study[7]. These findings were confirmed in a second study from Maryland, USA, in which outcome remained unchanged after adjustment for differences in patient populations[8].

A further point of discussion is the importance of the individual surgeon or the numbers of operations performed (surgeon volume) in comparison with the impact of specialist care and hospital facilities (hospital volume). Hospital volume and surgeon volume are often associated, but in most studies the individual surgeon and/or surgeon volume were not independent factors for outcome[3–8]. During the past 5 years the hospital mortality rate was 1·2 per cent in a consecutive series of 250 patients undergoing pancreatoduodenectomy in the present authors' institution. In that period four different surgical fellows undertaking supervised, advanced gastrointestinal surgical training performed around 50 resections without a single death.

Previous work has shown that pancreatic leakage is the most important determinant of mortality[9]. Its incidence is without doubt highly dependent on surgical technique and experience, but mortality after leakage may be reduced by

24-h specialist care and the aggressive management of postoperative complications; this requires a multidisciplinary approach. This aspect may be especially important, because it has been suggested recently that experienced surgeons should work in networks and perform high-risk surgery in low-volume hospitals. The problem of adequate management of postoperative complications, however, remains unsolved by such a network approach.

Most studies evaluating the relation of hospital volume and outcome of pancreatic surgery have focused on pancreatic resection, but recently it has also been shown that increased hospital volume is associated with a decreased hospital mortality rate for palliative bypass procedures and for stent insertion[8]. This phenomenon has been explained as a combined experience effect of the whole team. The authors concluded that all patients who are to be treated with curative or palliative procedures appear to benefit from referral to a high-volume provider[8]. An experience effect has also been reported in diagnosis. Reinterpretation of computed tomograms obtained elsewhere, by experienced radiologists in a tertiary referral centre, resulted in major discordant interpretations in 17 per cent[10]. This led to changes in treatment in 3 per cent of cases[10].

Should all patients with pancreatic carcinoma be managed in regional centres with high volume in the future? Those in favour argue that by doing so we will not only reduce the mortality rate after resection, but also after palliative treatment; the resection rate would probably increase and this could lead to a cost reduction[3]. It should, however, be noted that some individual surgeons have low mortality rates, even in low-volume hospitals[4]. Furthermore, the majority of patients with pancreatic carcinoma are not candidates for resection after state of the art selection and staging. After a limited diagnostic assessment these patients should undergo simple but adequate palliative treatment for the most common debilitating symptoms, such as obstructive jaundice, pain and gastric outlet obstruction. Such treatment has virtually no impact on the median survival of 4–5 months, and supportive care in the last months of life should preferably be offered near to relatives and friends. Unfortunately, the outcome of such aspects in terms of functional status and quality of life is not available from the studies described above and no conclusion can be drawn from the single study on palliative treatment[8].

Centralization of surgery for periampullary malignancy in the new millenium probably does not mean the regionalization of management of all patients. Experience from previous studies on diagnostic assessment and treatment in central hospitals might permit guidelines outlining a simple, standarized, well coordinated, noninvasive diagnostic approach, preferably with spiral computed tomography. Findings could then be accessed at a distance by modern communications to allow interpretation by specialized multidisciplinary teams. The majority of the patient population (60–70 per cent) could be selected for operative or non-operative palliative care, which should preferably be performed in community hospitals or by 1-day referral (stent insertion) to central hospitals. Only patients who are candidates for pancreatoduodenectomy, or who want to participate in new treatment modalities such as adjuvant chemotherapy or gene therapy, need to be brought to central institutions where they will probably benefit. Such a concept will have important implications for the organization of care.

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Anal intraepithelial neoplasia

A 40-year-old woman presents with anal bleeding, small haemorrhoids and fleshy anal skin tags, and is treated by haemorrhoidectomy. At operation, the skin tags appear slightly unusual; one is submitted to histological examination which shows the squamous epithelium to be hyperkeratotic and to contain areas of severe dysplasia. How should this patient be managed? Mr John Scholefield of Nottingham replies.

Although the terms 'dysplasia' and 'intraepithelial neoplasia' are not strictly equivalent, they are used as such throughout the literature on anal intraepithelial neoplasia (AIN). The term 'high-grade' dysplasia is equivalent to AIN III. 'Low-grade' dysplasia is equivalent to AIN I or II[1,2]. Some authors have classified perianal AIN lesions as PAIN, but the anatomical distinction between the perianal and anal canal skin is indistinct, and there seems little point in making this subdivision. The blanket term of AIN is preferred.

An incidental finding of AIN is most likely to arise in a haemorrhoidectomy specimen, such as that described above. Fenger and Nielsen[3] reported AIN in 10 per cent of haemorrhoidectomy specimens after very thorough histological examination. Most of these lesions are mildly dysplastic (AIN I) and require no further intervention. The distinction between features of papillomavirus infection and mild dysplasia is subjective and so interobserver and intraobserver biases are common[3]. While it is probably impractical and unnecessary to send all haemorrhoidectomy specimens for histopathological examination, surgeons should have a low threshold for such examination of specimens that appear macroscopically unusual. A history of systemic immunosuppression or other genital intraepithelial neoplasia should increase suspicion[4].

Since the malignant potential of mild or moderately dysplastic (AIN I or AIN II) lesions is likely to be extremely low it is reasonable to discharge a patient from follow-up in certain circumstances. If clinical examination raises doubts about the possibility of more severe dysplasia, examination under anaesthesia and biopsy of the affected areas are advised[5]. Patients who have had anal condylomata treated by podophyllin or trichloracetic acid seem to have a high incidence of low-grade dysplasia in excised tissue which may result from the chemical agents themselves. However, there is no evidence that these lesions progress to AIN III; they probably regress once the noxious chemical is no longer required. It is essential to discover whether women with AIN have a history of genital malignancy, or have had treatment for cervical intraepithelial neoplasia or vaginal intraepithelial neoplasia. If there is no such history, referral to a gynaecologist for genital colposcopy is advisable[2,6–8]. Most patients with AIN I or II can probably be discharged safely after 12 months' observation and one or two repeat examinations, provided the area appears stable and unchanged over this period.

If a severely dysplastic (AIN III) area is identified in a routine haemorrhoidectomy specimen or other anal biopsy, as in the present case, it is necessary to re-examine the area when the wounds have had time to heal. Occasionally an invasive lesion is under-reported and a persistent ulcerated area 2 months after the original procedure should lead to rebiopsy of the area. If the area has healed fully, a thorough inspection of the rest of the anogenital region (with the addition of anal cytology where possible) should identify any remaining severely dysplastic lesions[8]. If there is concern about further areas of AIN III in the perianal skin or anal canal (or where excision was incomplete), examination under anaesthesia with multiple targeted punch biopsies of the perianal and anal canal skin should be carried out. A disposable corneal punch (2, 3 or 4 mm) is very useful for this purpose.

Isolated small foci of AIN III may be locally excised and such excision of the perianal and anal canal skin can be justified where the area excised constitutes less than 40 per cent of the perianal region. However, such excisions may leave behind sites of AIN and there is likely to be a recurrence rate of at least 30 per cent over 5 years[9]. Long-term recurrence figures may be even higher as surgical excision is very unlikely to eradicate the underlying papillomavirus infection; individual susceptibility to this type of lesion makes recurrence probable in time. Although the time course of the disease process is uncertain, it is thought that it takes 5 years or more to progress from wart virus infection to high-grade AIN. This time course may be foreshortened in the immunosuppressed[4].

Multifocal AIN represents a difficult clinical problem[2,5]. In my experience over 70 per cent of women with AIN III have a previous history of cervical or vulval intraepithelial neoplasia. It is important to consider the genital tract in association with AIN III as the anal disease is contiguous with vulval dysplasia in many cases, and management of the genital disease needs to be taken into account when planning treatment for AIN[1,7]. Although wide excision of affected anal skin with the use of skin grafts or advancement flaps has been advocated for extensive AIN, these procedures often require temporary stomas and are associated with significant operative morbidity[5]. The reason for this type of radical surgery was a concern that AIN III might progress rapidly to invasive anal cancer. This notion does not appear to have been borne out and an observational strategy may be more appropriate given that the malignant potential of AIN III appears to be lower than was at first feared.

If the presence of widespread residual AIN III is established, a policy of observation at intervals of 6 months can be advocated. Repeated observation should be undertaken by a coloproctologist with experience of managing AIN. The most obvious sign of disease progression from AIN to invasive disease is ulceration.

Other modalities of treatment, including laser ablation and cryotherapy, have been suggested as possible treatments for AIN. Since these treatments destroy tissue they make it difficult to assess the extent and severity of disease. Furthermore, one of the characteristics of AIN and vaginal intraepithelial neoplasia is that the dysplasia also affects hair shaft and sweat gland epithelium, making ablational treatments liable to leave residual foci of disease which may lead to early recurrence[10]. Topical antiviral agents, such as interferons, may have a role in treating papillomavirus infection but there is little evidence to support their use in genital or anal dysplasia.

Oral and topical retinoids have been used in the treatment of genital intraepithelial neoplasia with mixed results. These drugs are unpleasant to take and compliance is often poor. My experience in a small number of cases has been disappointing owing to drug toxicity; side-effects include hepatotoxicity, myelosuppression and skin eruptions. Limited experience with topical retinoids in treating AIN precludes reliable assessment.

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Review

Popliteal artery entrapment syndrome

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Background: Popliteal artery entrapment syndrome (PAES) is rare and may be underdiagnosed. Improved specialized, non-invasive imaging techniques are producing detailed topographical evidence of the anomaly.

Methods: A historical review of the literature and Medline search was performed with reference to the diagnosis and treatment of the condition. In addition, embryologically based theories for the condition have been postulated.

Results and conclusion: PAES may be the result of abnormal development of the popliteal artery or a consequence of excessive cranial migration of the medial head of the gastrocnemius muscle. Magnetic resonance imaging appears to be the most useful single investigation to demonstrate the anomaly. Popliteal artery release alone or with vein bypass is the treatment of choice when intervention is indicated.

Paper accepted 6 July 1999

British Journal of Surgery 1999, 86, 1365–1370

Introduction

Angiography has been the investigation of choice in patients presenting with infrainguinal arterial occlusive disease, including popliteal artery entrapment syndrome (PAES). In recent years, attention has focused on the use of special imaging techniques, in particular magnetic resonance imaging (MRI). PAES is an uncommon condition that is easy to miss and so is probably underdiagnosed. This article reviews PAES; it includes the embryology of the arterial supply to the leg and the non-invasive imaging techniques now used in the diagnosis of the condition.

Background

In 1879, T. P. Anderson Stuart, an Edinburgh medical student, described an anatomical variant of the popliteal artery which he had dissected from a gangrenous limb[1]. The significance of this anomaly was not recognized until 1959 when Hamming and Vink[2] in the Netherlands described the clinical syndrome which is associated with entrapment of the popliteal artery. In their study of 1200 patients suffering from calf and foot claudication, 12 (1 per cent) were less than 30 years of age and five of these had PAES. Since then, a small number of series have been reported[3–8] but only 400 patients have been described in the English literature. Gibson *et al.*[9] described the anomaly in four (5 per cent) of 86 autopsy specimens. In a review of 20 000 asymptomatic Greek soldiers, Bouhoutsos and Daskalakis[10] found 45 affected limbs in 33 patients (0·17 per cent), leading them to conclude that only a small proportion of cases gives rise to symptoms.

Symptoms may be vague. In one series, claudication was the only symptom in 65 per cent of patients, with paraesthesia in 14 per cent and rest pain or trophic changes in 11 per cent[3]. Cramp after intensive physical training may be the dominant feature[11], but bizarre aching and numbness in the foot and calf may be the only symptoms in some. As the condition is more common in men, possibly owing to their superior muscular development[12], calf claudication in a young man should suggest popliteal entrapment[13]. Overtraining alone, however, may produce a similar syndrome in athletes, resulting from compression of the artery by hypertrophic soleus and plantaris muscles[14]. If PAES has been diagnosed in one limb, the contralateral limb should be screened[15–17]. PAES has been demonstrated in a pair of monozygotic twins[15] and a familial tendency has also been reported[18].

Embryology of the popliteal fossa

The arterial system of the leg develops from two embryonic arteries, both of which take origin from the umbilical artery,

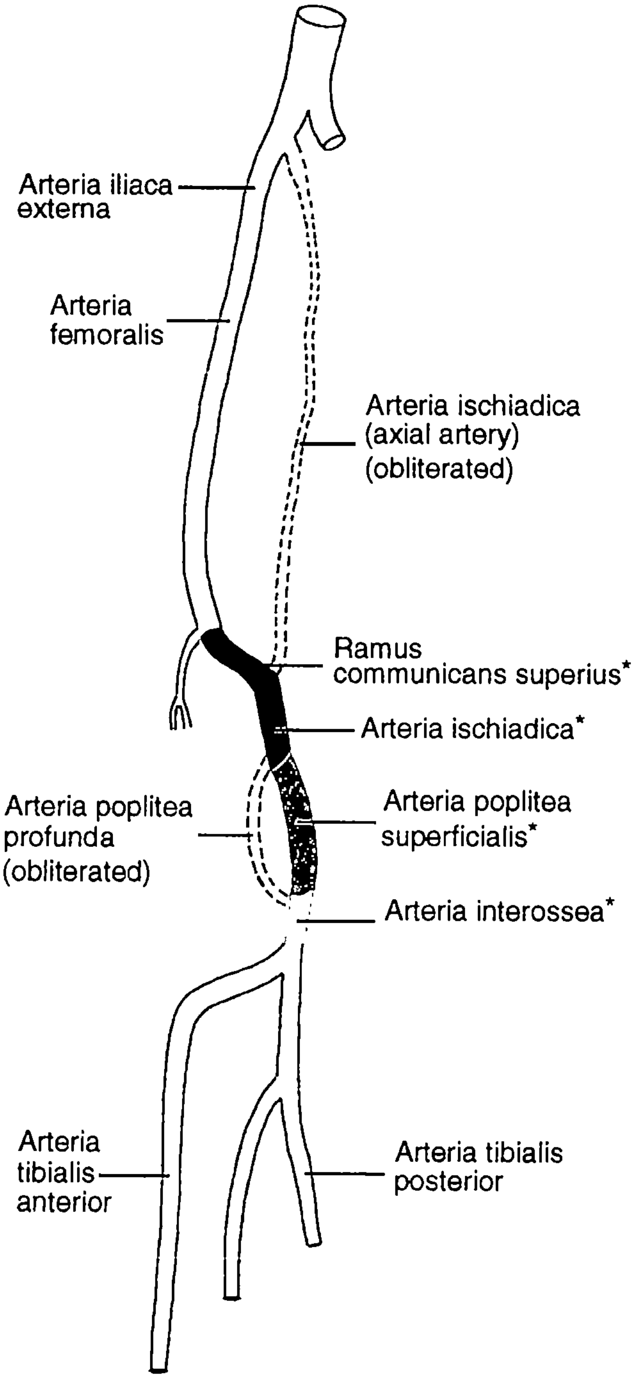
Arteria iliaca externa
Arteria femoralis
Arteria ischiadica (axial artery) (obliterated)
Ramus communicans superius*
Arteria ischiadica*
Arteria poplitea profunda (obliterated)
Arteria poplitea superficialis*
Arteria interossea*
Arteria tibialis anterior
Arteria tibialis posterior

Fig. 1 Schematic representation of the embryonic elements of the popliteal artery. *Embryological components of the adult popliteal artery

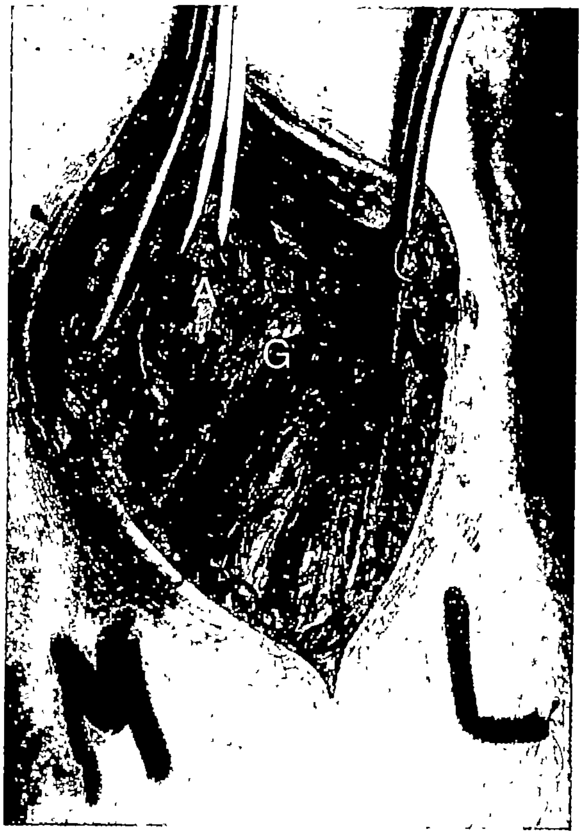

Fig. 2 Intraoperative photograph demonstrating the popliteal artery (A) displaced medially by an abnormal slip of the medial head of gastrocnemius (G)

a branch of the dorsal aorta[19]. Of the two embryonic arteries, the primal and principal one is the axial artery, first identifiable in the 5–6-mm embryo (30 days intrauterine life (i.u.l.)). The other is the external iliac artery that appears in the 8-mm embryo (32 days i.u.l.) and subsequently gives rise to the femoral artery when the embryo reaches the 11–12-mm stage (38 days i.u.l.). The axial artery runs longitudinally within the posterior (flexor) compartment of the developing lower limb, while the femoral artery elongates in the anterior (extensor) compartment. In its course behind the knee, the axial artery lies deep to the developing popliteus muscle; this is noticeable in the 14-mm embryo (42 days i.u.l.). At this stage the axial artery may be divided for descriptive purposes into three segments: proximal to, deep to, and distal to the popliteus muscle. The proximal segment is termed the arteria ischiadica, the middle segment the arteria poplitea profunda and the distal segment the arteria interossea. At this stage a bridging vessel, the ramus communicans superius, enters the popliteal fossa through the adductor hiatus, acting as a conduit between the femoral artery and the arteria ischiadica. At the 18-mm stage (48 days i.u.l.), the arteria ischiadica gives rise to a branch at a point just proximal to the upper border of the popliteus muscle. This vessel runs superficial to the popliteus muscle and is called the arteria poplitea superficialis; distally it joins the arteria interossea

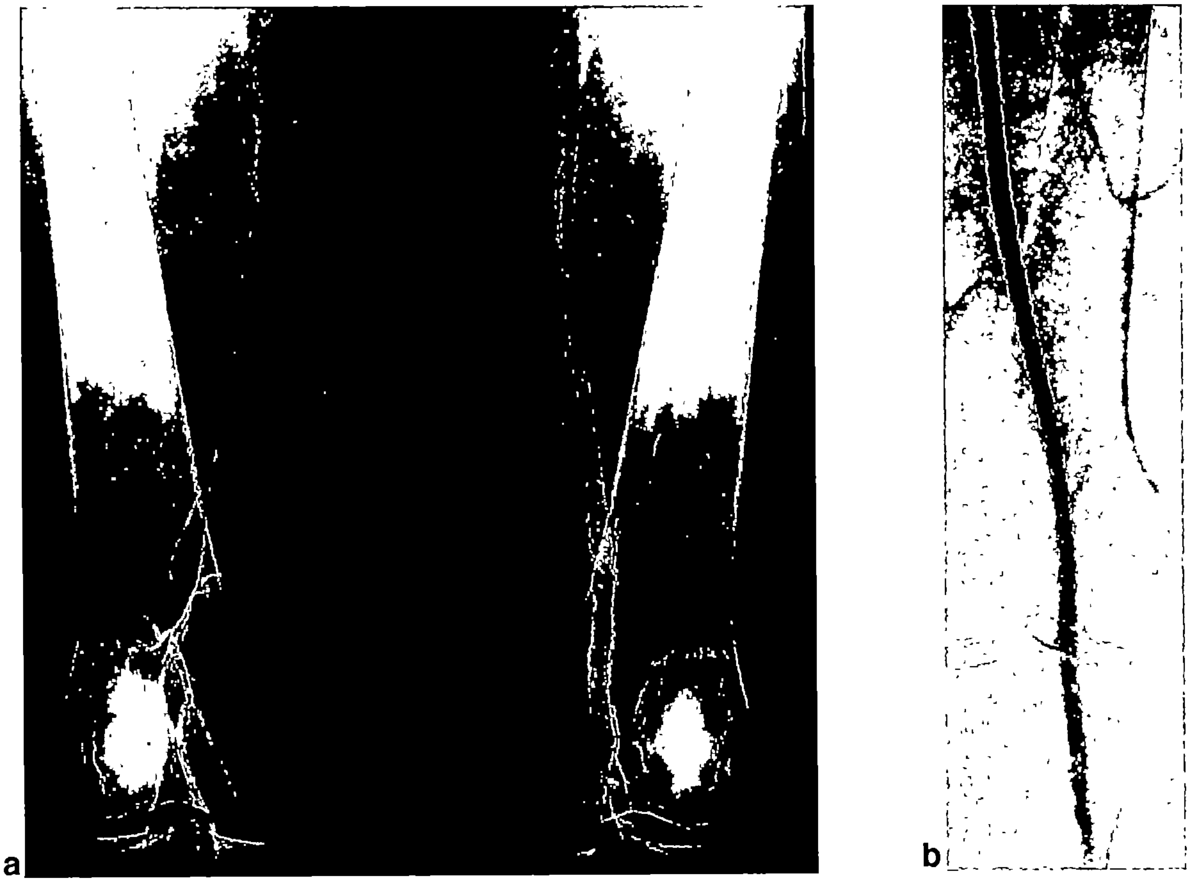

Fig. 3
a Angiogram of a patient with bilateral popliteal artery entrapment demonstrating medial displacement of the popliteal artery on the left (asymptomatic) and occlusion of the popliteal artery on the right (symptomatic).
b Normal left popliteal angiogram

which develops into the posterior tibial and peroneal arteries. With time, the arteria poplitea profunda becomes obliterated. The normal adult popliteal artery is, therefore, the product of fusion of several embryonic elements. From proximal to distal these are the ramus communicans superius, arteria ischiadica, arteria poplitea superficialis and the arteria interossea (*Fig. 1*).

Both heads of the gastrocnemius muscle arise from the femoral epiphysis. As the infant develops and progresses through the crawling to walking phase, the origins of this muscle migrate cranially across the epiphysial plate on to the femoral metaphysis. As a result of differential movement of the two heads of gastrocnemius, the medial head eventually comes to lie in a more proximal position on the femoral shaft than the lateral head. The origin of the medial head of gastrocnemius in the adult lies directly caudal to the adductor hiatus, with the popliteal artery lying immediately lateral to it.

On an embryological basis, PAES may be the result of the abnormal development of the popliteal artery due to persistence of the arteria poplitea profunda. This manifests itself in the popliteal artery lying deep to the popliteus muscle. Alternatively, the condition may be the consequence of excessive cranial migration of the medial head of gastrocnemius along the femoral shaft. This results in the adult artery lying medial to the medial head of gastrocnemius, or indeed passing through it. Several classifications of a number of anatomical variants of PAES have been described[7,10,20,21]. In the commonest of these, the popliteal artery enters the popliteal fossa by curving medial to the medial head of gastrocnemius (*Fig. 2*). The artery then courses laterally, deep to the medial head, between the latter and the underlying medial condyle of the femur. In other variants, a slip of gastrocnemius, a fibrous band or the popliteus muscle may cause constriction of the artery. Typically the artery alone is affected, but in one study it was

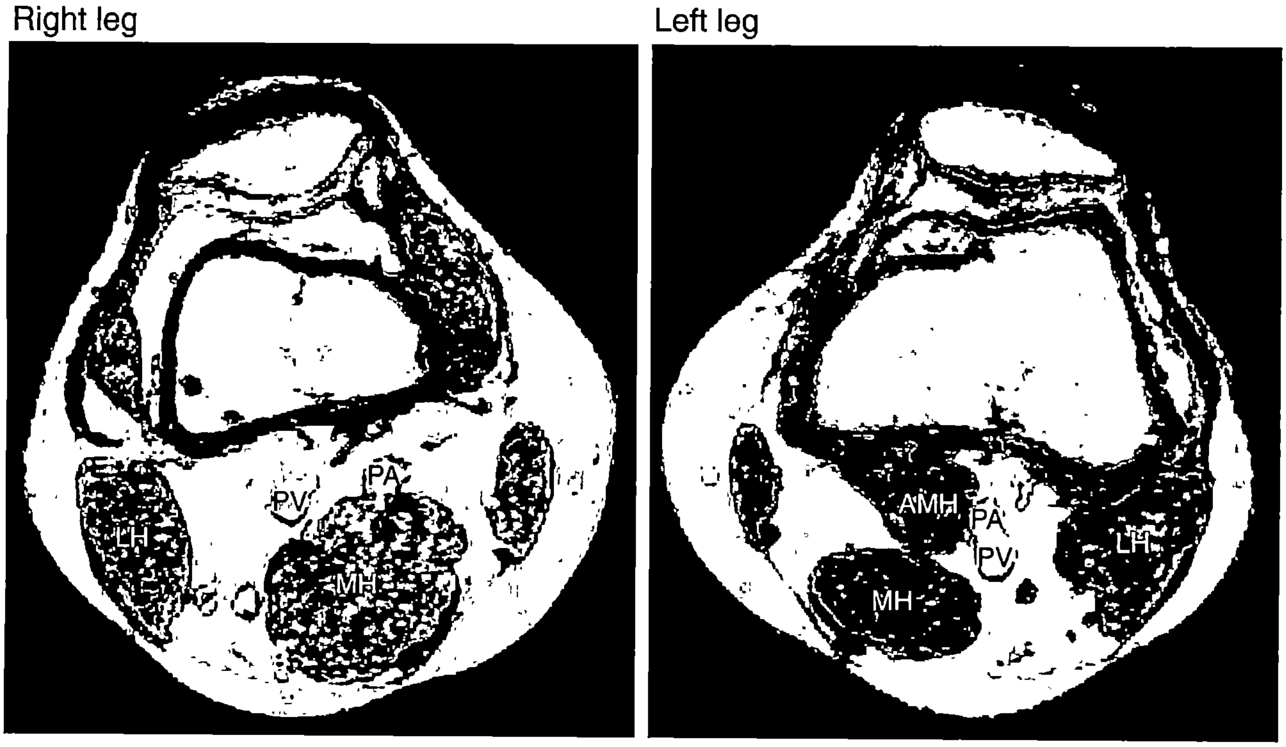

Fig. 4 Magnetic resonance images demonstrating the cross-sectional anatomy of the popliteal fossa in a patient with left-sided popliteal artery entrapment syndrome. The normal relationship between the popliteal vessels and the normal gastrocnemius muscle is seen in the right leg, with an abnormal medial head impinging on the vessels in the left. LH, lateral head of gastrocnemius; MH, medial head of gastrocnemius; AMH, abnormal medial head; PA, popliteal artery; PV, popliteal vein. (By courtesy of Mr J. J. Earnshaw)

observed that the popliteal vein was also involved in 8 per cent of patients[3]. It is also possible for the popliteal artery to undergo compression without an embryological anomaly being present. This condition, termed physiological PAES, may be due to a hypertrophied gastrocnemius, soleus, plantaris or semimembranosus muscle causing vascular compression and is sometimes seen in highly trained athletes[9,14,22,23].

Diagnosis and investigations

In severe cases, clinical examination may suggest an occluded popliteal segment but if the artery is still patent, there may be few clues. The disappearance of the pedal pulses while plantar flexing against resistance does not appear to be as reliable a clinical screening test as once thought[24]. If demonstrated, it should raise suspicion. It is important to include PAES on the list of differential diagnoses in young patients presenting to a vascular clinic with lower limb ischaemia. Much of the recent literature focuses on the difficulties in making the diagnosis. Where the popliteal artery is patent, the diagnosis can be made by angiography (*Fig. 3*), if the artery is displaced medially[25]. If the artery is patent but compressed, as in other variants of the syndrome, angiography may not demonstrate any deviation. If demonstrated, irregularity of the wall of the popliteal artery in an otherwise normal arterial tree should raise suspicion, especially if associated with prestenotic or poststenotic dilatation[26,27]. In 53 per cent of patients, there is occlusion of the popliteal artery at the time of presentation[3].

In 1991, di Marzo *et al.*[28] described the use of duplex ultrasonography in screening. Their technique involved insonation of the popliteal artery while carrying out active plantar flexion of the foot against resistance and with the knee flexed to 15°. A decrease in peak systolic flow in the popliteal artery was considered to be diagnostic. Unfortunately, the test gives an unacceptably high rate of false-positive results, particularly in athletes[22–24]. Computed tomography (CT) has been shown to be of use in the diagnosis and management of PAES[29,30]. In addition, CT has demonstrated adventitial cysts of the popliteal artery in a young man who was thought to have PAES[31]. Limb blood flow measured by isotope scanning has been used but its value is questionable[32,33].

MRI (*Fig. 4*) has increasingly been recognized to have an important role in demonstrating the abnormal relationship between the medial head of gastrocnemius and the popliteal artery[34–36]. Magnetic resonance tomography has been shown to be superior to duplex imaging and CT[37], with results similar to those of digital subtraction angiography[38] in defining the exact abnormality in PAES. It has been suggested, therefore, that MRI is an ideal screening test for PAES before angiography or surgery[39]. MRI techniques are particularly useful when the popliteal artery is occluded, in which situation duplex scanning and angiography are of limited value. The combined morphological and functional evaluation of the popliteal fossa makes MRI the investigation of choice in the management of young adults with intermittent claudication[40].

Treatment

The management of a patient with PAES depends on the clinical picture. Ideally, if the vessel remains undamaged, simple release of the popliteal artery by division of the medial head of gastrocnemius or other abnormal slips of muscle and tendon may be all that is required[8]. Reconstruction of the divided muscles does not appear to be necessary. Balloon angioplasty following thrombolysis has been reported but the rationale is unclear and the results unpredictable[5,41]. A damaged or occluded artery requires reconstruction. Thromboendarterectomy and vein patching may seem an attractive option but this appears to give inferior results compared with interposition grafting using vein[13].

Where the artery is occluded, bypass is superior to local therapy. If a short popliteal occlusion is present, revascularization may be carried out using the posterior approach with the patient in the prone position[7,8]. Good access is afforded to the artery and other structures of the popliteal fossa, facilitating both confirmation of the diagnosis and popliteal artery release. Furthermore, using this approach a suitable short saphenous vein may be used as an interposition graft. The medial approach to the popliteal artery is better for longer occlusions that need femoropopliteal bypass. One technical disadvantage of this approach, however, is that complete exposure of the popliteal artery and its relationship to the surrounding muscle is difficult; this can lead to the underlying entrapment being missed.

Conclusions

Popliteal artery entrapment, although rare, is probably underdiagnosed. It should be included in the differential diagnosis of acute popliteal artery occlusion, claudication or bizarre leg pains in young patients, especially men. Prompt diagnosis enables treatment before arterial occlusion; a missed diagnosis may have serious long-term consequences in a young patient. MRI appears to be the most useful single investigation in the diagnosis of PAES but each imaging modality has its place and it may be appropriate to use several in combination to make a firm diagnosis. Popliteal artery release alone or with vein bypass is the treatment of choice when intervention is indicated.

Acknowledgements

The authors acknowledge the help of Dr V. Mahadevan, Barbers' Company Reader in Anatomy, The Royal College of Surgeons of England in the preparation of this manuscript.

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Review

Surgical management of severe secondary peritonitis

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Background: Despite advances in diagnosis, surgery, antimicrobial therapy and intensive care support, the mortality rate associated with severe secondary peritonitis remains unacceptably high. This article presents various surgical treatment strategies for severe secondary peritonitis, emphasizing the role of open management of the abdomen and planned relaparotomies.

Methods: Material was identified from previous review articles, references cited in original papers and a Medline search of the literature.

Results and conclusion: Surgical treatment of severe secondary peritonitis is highly demanding and very complex. The combination of improved surgical techniques, antimicrobial therapy and intensive care support has improved the outcome of such peritonitis following perforation or anastomotic disruption of the digestive tract, or infected necrotizing pancreatitis. However, aggressive surgical treatment strategies, such as open management of the abdomen and planned relaparotomies, may have reached their limits.

Paper accepted 6 July 1999

British Journal of Surgery 1999, 86, 1371–1377

Introduction

Despite advances in diagnosis, surgery, antimicrobial therapy and intensive care support, severe secondary peritonitis remains a potentially fatal affliction. Although greater understanding of the pathophysiology of intra-abdominal infections, the introduction of timed surgical or radiological intervention, and improvement in critical care have reduced the mortality rate associated with severe intra-abdominal infections, the rate remains unacceptably high.

In an effort to improve the results of treatment of severe secondary peritonitis, new operative techniques such as planned relaparotomies and laparostomies have been introduced, especially in cases of severe bacterial peritonitis following perforation or anastomotic disruption of the digestive tract and infected necrotizing pancreatitis. It is clear that the modern surgical management of patients who are critically ill from severe intra-abdominal infections requires careful decision making. The purpose of this review is to present various therapeutic regimens for severe secondary peritonitis, especially emphasizing the role of open management of the abdomen and planned reoperations for this surgical challenge.

Definition, classification and stratification of intra-abdominal infections

Intra-abdominal infections have two major manifestations: bacterial peritonitis and its late but localized stage, intra-abdominal abscess. Bacterial peritonitis can be classified into primary, secondary and tertiary peritonitis. Primary peritonitis is usually defined as a diffuse bacterial infection of the peritoneal cavity occurring without loss of integrity of the digestive tract; the rarity of a polymicrobial infection is in marked contrast with secondary peritonitis. Secondary bacterial peritonitis is defined as an acute infection of the peritoneal cavity, usually resulting from perforation or anastomotic disruption of the digestive tract, or infected necrotizing pancreatitis. When timely surgical treatment combined with appropriate antimicrobial therapy is undertaken, most patients are able to resolve the infection. However, when patients are unable to contain the infection, whether because of an overwhelming infection and/or impaired defence mechanisms, tertiary peritonitis develops, a diffuse and persistent form of peritonitis that is often fatal. When patients are able to localize the infection, an intra-abdominal abscess develops[1–3].

The multifaceted nature of severe intra-abdominal infection makes it difficult precisely to define the disease and its severity, and to evaluate and compare different therapeutic surgical treatment policies[4]. However, it is well known that both the anatomical source of the problem and its physiological derangement affect the outcome of the intra-abdominal infection[5]. Meakins *et al.*[6] proposed a classification system incorporating both the anatomical source of the infection and its physiological compromise measured using the acute physiological score, part of the Acute Physiology And Chronic Health Evaluation (APACHE) scoring system. However, a multicentre study examining this surgical infection stratification system showed that acute physiological score, malnutrition and age were most noteworthy for predicting outcome, whereas aetiology of the infection contributed only slightly[7,8]. In 1988, Bohnen *et al.*[9] showed that the APACHE II scoring system, measuring the severity of disease, age and chronic health status of the patient, was of great value in predicting outcome and stratification of patients with intra-abdominal infection. The APACHE II score was independently associated with the rate of mortality. For example, patients treated for abdominal sepsis with an APACHE II score of 21–25 had a risk of death of about 50 per cent[9,10]. The Surgical Infection Society adopted the APACHE II scoring system as the best available (although not ideal) method of risk stratification in intra-abdominal infection[11].

Microbiology of intra-abdominal infections

In primary peritonitis, bacteriological cultures of the peritoneal fluid usually reveal a monomicrobial, aerobic infection. It classically occurs in young girls and is caused by *Streptococcus pneumoniae*[12]. In adults, the presence of alcoholic cirrhosis and ascites is the most frequently encountered underlying risk factor[13]. In most patients with cirrhosis, bacteriological cultures grow *Escherichia coli*[14]. Anaerobes are rare; the presence of aerobes and anaerobes suggests secondary peritonitis. In secondary peritonitis, the infection is most commonly polymicrobial with an average of four isolates per patient, with the most frequently encountered combination being *E. coli* and *Bacteroides fragilis*[15]. The number and types of bacteria increase progressively down the digestive tract with the largest concentration of bacteria in the distal colon. In cases of perforation of the oesophagus and stomach, Gram-positive micro-organisms predominate. When perforations occur more distally, Gram-negative and anaerobic isolates are more frequently encountered. In the colon, 1 g of stool contains up to 10^{12} anaerobes and 10^{8} aerobes. After perforation of the colon, more then 400 different species of bacteria invade the peritoneal cavity, although only a few are involved in the ensuing infection[16–20].

In tertiary peritonitis, *Staphylococcus epidermidis*, *Pseudomonas* spp. and *Candida* spp. are the predominant micro-organisms. *E. coli* and *B. fragilis*, the predominant bacteria in secondary peritonitis, are only occasionally found. The probable source of these micro-organisms is the patient's own digestive tract[21,22].

Experimental models of peritonitis

The pathophysiological mechanisms of peritonitis are poorly understood and so experimental models have been designed in an attempt to simulate the natural sequence of events occurring in humans. By 1974, Bartlett *et al.*[23,24] had developed an experimental model of intra-abdominal infection in rats mimicking human disease in its progression to formation of intra-abdominal abscesses. They demonstrated that Gram-negative aerobes such as *E. coli* are responsible for the early deaths associated with severe intra-abdominal infection. Later, a synergistic interaction between both aerobes and anaerobes is necessary to produce intra-abdominal abscesses[25]. Consequently, commencing both antiaerobic and antianaerobic therapy reduced the early mortality rate as well as formation of abscesses[26,27]. Therefore, in general, both antiaerobic and antianaerobic agents should be used from the beginning of secondary peritonitis in human disease.

Surgical management of severe secondary peritonitis

The surgical management of severe secondary peritonitis is based on three fundamental principles: (1) elimination of the source of infection, (2) reduction of bacterial contamination of the peritoneal cavity and (3) prevention of persistent or recurrent intra-abdominal infection.

Source control

In general, the operative approach and the surgical strategy depend on the source of the infection, the degree of contamination of the peritoneal cavity, the current condition of the patient and his or her premorbid health status. Traditionally, severe secondary peritonitis has been approached by performing a midline laparotomy to identify and eliminate the source of peritonitis. This midline approach permits the surgeon to perform a thorough and complete cleansing of the peritoneal cavity in order to reduce the bacterial contamination. Ongoing contamination is controlled by closure, exclusion or resection of the infective focus. In certain instances complete control of the infective source is not feasible during the first operation, for example in infected necrotizing pancreatitis.

Controversy exists regarding the surgical management of perforation of the left colon, most often occurring as a result of diverticulitis or sigmoid carcinoma. Optimal management is accomplished by resecting the perforated segment and exteriorizing the proximal end as an end-colostomy, dealing with the distal end by creating a mucous fistula or by simple closure (Hartmann's procedure). The generally held concept is that a primary anastomosis in a strongly contaminated peritoneal cavity is at high risk of dehiscence and should therefore be avoided[28,29]. However, this general concept has been challenged more than once and further testing in a controlled clinical trial is being undertaken to define those patients most likely to benefit from primary anastomosis[30,31]. While the risk of dehiscence of a primary anastomosis of the small intestine is much lower, in circumstances of extensive contamination of the peritoneal cavity or concern about the viability of the intestine, resection and enterostomy should be performed.

Reduction of bacterial contamination

The second goal of surgical management of severe secondary peritonitis is achieved by aspiration of all gross purulent exudates and removal of faecal debris or food particles. Pelvic regions, paracolic gutters and subphrenic spaces must be opened and debrided. Radical peritoneal debridement, as described by Hudspeth[32] in 1975, including removal of fibrinous deposits from the parietal and visceral peritoneal surfaces, has not lived up to early expectations. In 1980, a randomized trial in which this technique was compared with the standard method demonstrated no advantage[33]; on the contrary, radical mechanical debridement caused excessive bleeding and probably endangered the integrity of the intestine.

Intraoperative peritoneal lavage with saline, on the other hand, is performed regularly by most surgeons to reduce the degree of bacterial contamination and to remove blood, faecal material and necrotic tissue[34]. Its efficacy, however, is not well documented; there is no real evidence that intraoperative peritoneal lavage reduces the mortality rate or the incidence of septic complications in patients receiving adequate systemic bacterial therapy. The addition of antibiotics to the lavage solution appears to be without clear benefit; the addition of antiseptics may even produce toxic effects[35,36]. In view of the lack of clear benefit, Nathens and Rotstein[18] have recommended that the lavage fluid be completely aspirated before closure of the abdomen.

Prevention of persistent or recurrent infection

Postoperative peritoneal lavage, intra-abdominal drains and relaparotomy have all been used to prevent persistent or recurrent infection. The role of continuous postoperative peritoneal lavage is questionable. In the early 1980s, such lavage received much attention and was installed frequently to reduce postoperative septic complications. At the end of the laparotomy, intra-abdominal drains were left in place and the peritoneal cavity was lavaged continuously until the effluent became clear. Antibiotics as well as low-dose heparin were added to the lavage solution to reduce further the risk of persistent or recurrent infection and to prevent the formation of fibrinous adhesions[37–39]. In 1987, however, Leiboff and Soroff[40] concluded that the clinical value of continuous postoperative peritoneal lavage remained unclear. Furthermore, postoperative peritoneal lavage is extremely labour intensive and can lead to complications related to the use of intra-abdominal drains, such as visceral or vascular erosion with fistula formation or bleeding. Besides, drains may act as a route for retrograde spread of infection into an otherwise sterile environment[41]. Haller *et al.*[42] demonstrated that children who had drains placed at the end of surgery for perforated appendicitis had a hospital stay that averaged 3·7 more days than that of those without drains. Drains should be used only to maintain drainage of abscesses, to allow the escape of visceral secretions, to control a fistula that cannot be exteriorized or to effect continuous postoperative peritoneal lavage[1,43].

Ideally, an intra-abdominal infection should be cured with a single operation. Unfortunately, intra-abdominal infection often persists or recurs in cases of severe secondary peritonitis. This led in the 1980s to the concept of the relaparotomy. It had become clear that waiting for the appearance of signs of persistent or recurrent infection or, in the worse cases, even development of multiple organ failure as an indication for a relaparotomy was futile[44,45]. In this belief (and later based on the finding that one extra laparotomy often fails to control persistent or recurrent intra-abdominal infection) relaparotomies and open management of the abdomen were introduced[46–69].

Planned relaparotomies, referred to as ‘etappenlavage’ in the German literature[49,50], constitute the cornerstone of aggressive surgical management of severe secondary peritonitis. Reoperations are performed at fixed intervals (24–72 h), irrespective of the patient's clinical condition, thereby preventing the development of new septic fluid collections and so precluding their deleterious systemic effects. Relaparotomy may be carried out under general anaesthesia in the operating room or in the intensive care unit. The purpose of each re-exploration is to evacuate all septic collections, to debride or even resect, until the surgeon decides to discontinue the re-explorations because the peritoneal cavity has become macroscopically clean. Planned reoperations also allow inspection of anastomoses constructed during earlier laparotomy. After the final laparotomy the patient's clinical condition is followed closely. If unexpected deterioration occurs, ultrasonography and/or computed tomography are performed. When necessary and possible, such imaging may be used to guide drainage procedures or surgical interventions. Adverse effects of planned relaparotomies are frequent and include damage to the abdominal wall structures and oedematous viscera, causing bleeding or even enteric fistulas.

Classically, open management of the abdomen or laparostomy involves leaving the abdominal wall open and packing the defect with saline-soaked gauzes[52,54,55]. A variety of techniques, including the use of non-absorbable meshes and/or transparent drapes, has been devised[53,57,70]. Open management has several advantages, based (at least theoretically) on sound surgical principles[63]. Its major advantages are facilitation of frequent re-exploration and, by treating the entire peritoneal cavity as one large infected collection, continuous exposure for maximal drainage. Furthermore, its application serves to decrease high intra-abdominal pressures, thereby treating the deleterious effects of the abdominal compartment syndrome[71]. However, the putative clinical benefits of the reduced intra-abdominal pressure, such as improved ventilation[72] and renal perfusion[73,74], remain unproven. Also the hypothesis that permanent exposure of the peritoneal cavity to open air promotes the control of intra-abdominal infection remains theoretical[52]. Schein[2] concluded in his review that open management of the abdomen only allows surgeons easy multiple re-entries with minimal additional damage of the abdominal wall. Open management of the abdomen should, therefore, be reserved for patients needing more than two reoperations and for those in whom closure of the abdominal wall is impossible.

Early complications of open management of the abdomen and frequent re-explorations include evisceration, massive losses of fluids, electrolytes and proteins, spontaneous enteric fistulas, and potential contamination of the open wound by exogenous organisms[65]. The use of a non-absorbable mesh and a covering transparent drape with suction tubes between the mesh and the drape (sandwich-technique), as described by Schein *et al.*[70], has managed these complications satisfactorily. A large number of other combinations of absorbable and non-absorbable meshes, zippers, slide fasteners and other devices has been advocated by many users and manufacturers[50,53,57,59,61,70]. Although a resorbable mesh can be used to cover an abdominal defect when no further re-exploration is deemed necessary, it cannot be used during frequent re-explorations because of the risk of early disintegration, resulting in complete intestinal evisceration[75,76]. In cases of abdominal wall defect, a ventral hernia will develop. In general, definitive repair of such a hernia should be delayed for some months and is usually performed at the time of restoration of continuity of the digestive tract[77].

It is not easy to assess precisely the benefits of open management of the abdomen, because it is not possible to compare this approach meaningfully with more conventional surgical strategies due to the heterogeneity of patients and underlying diseases. Furthermore, timing of application of the open approach and the variety of different techniques differ widely between centres. Initially, results of open management of the abdomen and planned reoperations applied in the early stages of the disease were promising, with mortality rates of 7 and 15 per cent[52,55]. Results in the treatment of infected pancreatic necrosis seemed especially promising[65,69]; Bradley[65] reported a mortality rate of 11 per cent in patients treated with open packing and frequent re-exploration. However, more recent studies have failed to reproduce these good results[59,64,66]. In a review of the literature, D'Egidio and Schein[78] evaluated the results of different treatment strategies applied in infected pancreatic necrosis, and concluded that survival rates for the open approach and closed treatment strategies supplemented by local lavage were identical. The incidence of surgical complications, such as fistulas or intestinal necrosis, however, was significantly higher in patients treated by open management than in those treated with closed techniques[51,78–80]. Therefore, it was concluded that the open approach should be used only in selected patients who need three or more relaparotomies, or in those whose abdomen cannot be closed[2,51,78–80].

In a review of the literature, Schein[2,51] showed that the overall mortality rate in 551 patients treated aggressively for intra-abdominal infection and sepsis was 32 per cent. In a prospective non-randomized study including 52 patients treated for critical intra-abdominal infections, it was concluded that open management of the abdomen may have been beneficial in patients treated for diffuse faecal peritonitis following perforation of the digestive tract[51]. In patients suffering from postoperative peritonitis owing to anastomotic disruption, however, the place of open management remained unclear[51]. A recently published, prospective non-randomized study, attempting to compare closed and open treatment strategies, failed to demonstrate any advantage of either treatment strategy over the other[81].

Another prospective study, comparing the concept of open management of the abdomen and planned reoperations, renamed as 'staged abdominal repair' (STAR), and more conventional surgical techniques, showed that in patients at equal risk of death the STAR approach was superior[82]. Nevertheless, a recent non-randomized study failed to demonstrate the assumed benefits of planned relaparotomies[83]. In the near future, an ongoing prospective randomized multicentre study will further document the effect of these aggressive treatment strategies[84,85].

It is clear that the combination of improved surgical techniques, antimicrobial therapy and intensive care support has improved the outcome of severe secondary peritonitis following perforation or anastomotic disruption of the digestive tract, or infected necrotizing pancreatitis. Surgical treatment of severe secondary peritonitis is highly demanding and very complex. Perhaps aggressive surgical treatment strategies in the critically ill have reached their limits. Only well documented prospective randomized trials, including a detailed description of patients and the severity of their disease, will allow a proper evaluation and comparison of the results of different treatment strategies.

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Digest

Professor Seiki Matsuno, Chief Editor of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the January to March 1999 issues of the journal for this quarter's digest. A digest of *BJS* for the same period written by Mr Colin Johnson, Development Officer, appears in the Japanese Journal.

Cardiac surgery

The surgical treatment of descending thoracic aortic anastomotic aneurysm is technically challenging[1]. This study was designed to evaluate the use of a temporary external bypass method as an intraoperative measure. An analysis of five consecutive patients who had undergone surgery for a total of seven descending thoracic aortic anastomotic aneurysms in the authors' university hospital over a period of 14 years was made. A temporary bypass technique was used as an intraoperative measure in all of the operations, four of which were performed with right axillary to left external iliac artery bypass, while other sites were used in the remaining three. Systemic heparinization was avoided in six operations and was markedly reduced in the remaining one. Although the major postoperative complication was coagulated haemothorax after six procedures, all patients recovered well and are still alive after a mean(s.e.m.) follow-up of 8·2(1·5) years. The authors concluded that their temporary bypass method for treating descending thoracic aortic anastomotic aneurysm prevented the risks of anticoagulant administration for circulatory support, which contributed to the success of the operation. This method can be used as adjunct treatment for anastomotic aneurysms in the descending thoracic aorta.

In a second study, a new ultrashort-acting β-blocker, ONO-1101, was administered during cardiopulmonary bypass (CPB) to investigate its effects on cardiac function and haemodynamics[2]. Nine adult mongrel dogs underwent 60 min of CPB during which they were given either ONO-1101 (ONO group; $n = 4$) or saline (control group; $n = 5$). In the ONO group, the hearts became flaccid enough for surgery to be performed without cardiac standstill within 10 min after the commencement of ONO-1101, with significant decreases in the heart rate, preload recruitable stroke work and the slope of the end-systolic left ventricular pressure–volume relationship (E_{max}). The mean arterial pressure and systemic vascular resistance also decreased, but were maintained above 50 mmHg during CPB without catecholamine. These indices increased to the control group level 20 min after the discontinuation of ONO-1101. The serum concentration of ONO-1101 decreased from the mean maximum level of 121 μg/ml soon after infusion to 11 μg/ml within 30 min of discontinuation. These data suggest that ONO-1101 may be useful in enabling beating-heart surgery to be performed without aortic cross-clamping.

Oesophagus

A phase II study was conducted to determine the clinical efficacy and toxicity of 5-fluorouracil (5-FU) and low-dose cisplatin (CDDP) in patients with squamous cell carcinoma of the oesophagus[3]. Chemotherapy consisted of 5-FU at a dose of 330 mg per m^2 per day, given as a 24-h infusion on days 1–7, and CDDP at a dose of 6 mg per m^2 per day given as a 2-h infusion on days 1–5. Either two or four cycles of chemotherapy were administered to 20 patients with stage III advanced oesophageal carcinoma. All 20 patients were then assessed for response and toxicity. An objective response was demonstrated in 11 of 20 patients, with one complete response and ten partial responses, bringing the response rate to 55 (95 per cent confidence interval 27–83) per cent. Surgical resection of the tumour was performed in all 20 patients. One patient was found to have a grade 3 histologically complete response. The median survival of all the patients was 20·5 (range 4·5–48·0) months. Neutropenia and thrombocytopenia developed in five and two patients respectively, and non-haematological toxicity was insignificant. The findings of this phase II study indicate that preoperative treatment using 5-FU and low-dose CDDP chemotherapy for patients with advanced oesophageal carcinoma appears to achieve a high response rate after short-term administration.

A study was conducted on 78 patients, encountered over a 7-year period, who had a catheter-feeding jejunostomy placed at the time of thoracoabdominal oesophagectomy for oesophageal cancer[4]. A broad-based attachment of the jejunal wall to the peritoneum at the place of entry of the catheter was used. Enteral nutrition was begun a mean of 10 days after the operation, the caloric content was increased gradually and the mean duration was 69 days. Three patients suffered from local skin erosion at the site of catheter entry and seven developed diarrhoea and/or a feeling of abdominal fullness, but no patient showed any signs of peritonitis or ileus. The morbidity rates related to enteral nutrients and placement of the catheter jejunostomy were 9 and 4 per cent respectively. These findings demonstrate that broad-based attachment of the jejunal wall to the peritoneum at the place of entry of the catheter is useful for preventing leakage or twisting of the jejunum, and for reducing the incidence and severity of the complications of catheter jejunostomy feeding.

Stomach

To elucidate efficacy in gastric surgery, the authors evaluated seven resected cases of submucosal gastric tumour in which laparoscopic techniques were used[5]. The patients consisted of one man and six women. The tumours were in the upper, middle and lower third of the stomach in four, one and two patients respectively. Three tumours were located mainly on the anterior gastric wall, two were on the posterior wall and two were on the lesser curvature. The resected tumour size was a mean of 3·2 × 2·6 cm. The tumours were classified as intraluminal type (four) and extraluminal type (three) according to the classification of growth type. Histopathological examination identified four leiomyomas, one leiomyosarcoma and two smooth muscle tumours of indeterminate malignant potential. After tumour resection, no recurrence of the lesions occurred during follow-up. A tumour growing extraluminally was easily resected by the laparoscopic method without any additional procedure; this seemed to be a good indication for the laparoscopic technique. In contrast, an intraluminal tumour was found to be more difficult to resect using the laparoscopic method without a companion procedure (e.g. intraoperative endoscopy) because of difficulties in the detection and resection of the tumour from the serosal side. A more efficient technique must, therefore, be developed for this type of tumour.

Although peritoneal lavage cytology is performed widely during surgery for gastric cancer and the result has been reported to be one of the accurate prognostic factors, the cancer stage is determined independently of the results of lavage cytology according to the First English Edition of the Japanese Classification of Gastric Carcinoma[6]. In this study, the authors demonstrate the validity of lavage cytology for accurately staging gastric cancer. Between 1988 and 1996, peritoneal lavage cytology was performed in 347 patients with resectable gastric cancer. Among them, the cytology was positive in 29 cases (8 per cent). The survival rate of the cytology-positive patients in each stage was worse than that of all patients in the same stage. The prognosis of patients with positive cytology findings and serosa-exposed gastric cancer was significantly worse than that of patients with negative cytology findings and serosa-exposed gastric cancer, and similar to that of those with negative cytology findings and serosa-infiltrating gastric cancer. These data suggest that positive cytology findings indicate a poor prognosis; the prognostic difference between positive and negative cytology was approximately a one-stage difference in the Japanese stage grouping. Based on these findings, the results of peritoneal lavage cytology should be included in the factors used for staging gastric cancer.

Colon and rectum

The correlation of nm23-H1 expression in primary cancer lesions with the 14 prognostic variables already confirmed and survival was examined in 52 patients with advanced colorectal cancer; the clinical role of nm23-H1 expression in the cancer lesions remains controversial[7]. Immunohistochemical expression of nm23-H1 was found in 23 lesions (positive group) but not in 29 (negative group). No significant difference between the positive and negative groups was found with respect to 12 clinicopathological variables, including vascular invasion, lymph node and liver metastases, and histological stage. The mean carcinoembryonic antigen level of the draining venous blood (21·5 ng/ml) and mean argyrophilic nucleolar region score of the cancer cells (3·35 per nucleus) in the positive group were not significantly different from those in the negative group (34·1 ng/ml and 3·32 per nucleus). In addition, no significant difference was found in the survival curves or the 5-year survival rates of the positive and negative groups. From these results, it may be concluded that nm23-H1 expression was not associated with the aforementioned prognostic variables and prognosis of patients with advanced colorectal cancer.

A total of 506 patients with distal colorectal cancer was divided into two groups to examine the variables affecting survival of patients with macroscopic invasion into adjacent organs; 47 showed invasion (invasive group) while the others did not (non-invasive group)[8]. Differences between the invasive and non-invasive groups were found in eight variables; female sex, large tumour size, gross type 3 and 4, moderately or poorly differentiated adenocarcinomas and signet-ring cell or mucinous carcinomas, deep cancer invasion, lymphatic invasion, peritoneal and liver metastases, and curability B–C were found significantly more frequently in the invasive group. The survival curve of the invasive group was significantly lower than that of the non-invasive group. However, no significant difference was found between the survival curves of the patients with curability A (no residual tumour) in both groups. A multivariate analysis in the invasive group revealed six variables to be related significantly to good prognosis, including young age, female sex, location above the peritoneal reflection, well differentiated adenocarcinoma, negative lymphatic invasion and curability A. Surgery with curability A should be performed to improve survival in distal colorectal cancer with macroscopic invasion into adjacent organs.

Liver

A study was undertaken to determine whether or not prostanoid metabolism contributes to peritonitis-induced early liver oxidant stress[9]. Lipid peroxidation products, malondialdehyde (MDA) and conjugated dienes (CDs) were used to monitor oxidant stress. Rats were given a 5-ml intraperitoneal injection of 25 per cent rat faeces suspension and then received either intraperitoneal saline (peritonitis group; $n = 11$), vitamin E ($n = 6$) or diclofenac ($n = 6$). The liver and plasma MDA and CD levels were measured after 3 h. The plasma and liver MDA and CD levels were significantly higher in the peritonitis group than in the control group ($n = 9$). Prostaglandin synthetase inhibitor (diclofenac) kept the liver and plasma MDA and CD concentrations at control levels. The antioxidant α-tocopherol (vitamin E) was found not to be effective in reducing MDA and CD levels. Peritonitis-induced early oxidant stress in the liver seems to be mediated by oxidant-independent activation of the cyclo-oxygenase pathway.

Pancreas

To investigate the prognostic factors associated with pancreatic cancer, a retrospective analysis of 193 patients who underwent curative resection was conducted[10]. Of these 193 patients, 38 (20 per cent) survived for more than 5 years; the 5-year survival rates for stages I, II, III and IV disease were 41, 17, 11 and 6 per cent respectively. According to a multivariate analysis, lymph node metastasis, intrapancreatic perineural invasion and portal vein invasion were significant prognostic factors. A subgroup analysis concerning nodal metastasis and intrapancreatic perineural invasion was performed in 126 patients with records of these histological findings. In the group of patients without nodal metastasis, the 5-year survival rate for those without perineural invasion was 75 per cent, whereas that for those with perineural invasion was 29 per cent ($P < 0.02$). In the group of patients with nodal metastasis, the 5-year survival rate for those without perineural invasion was 17 per cent, while that for those with perineural invasion was 10 per cent. The most favourable 5-year survival rate of 89 per cent was observed in the subgroup of patients with stage I disease without perineural invasion. Thus, patients with pancreatic adenocarcinoma, categorized by the combination of these independent types of biological behaviour, had 5-year survival rates ranging from very high to low, indicating that these two factors play an important role in the prognosis of the disease.

Islet cell carcinoma of the pancreas is a rare, indolent malignancy associated with a higher resectability rate and better survival than ductal carcinoma[11]. This retrospective study presented the results of surgical treatment for non-functioning islet cell carcinoma in seven patients. There were two men and five women, with a mean age of 54 years. Of the seven tumours, four were located in the head of the pancreas and the other three in the body or tail. Epigastric pain was frequently the primary clinical symptom. By the time of diagnosis, four of the patients had regional disease (one had lymph node and liver metastases and one had liver metastases). Another patient was found to have lymph node metastases at operation. Only one of the patients died from recurrent cancer, 21 years after the original operation. All of the patients who had liver metastases at the time of initial surgical treatment are now living at home. The authors concluded that non-functioning islet cell carcinomas are slow-growing tumours with a good prognosis if the main tumour and metastatic lesions are removed.

Thyroid gland

Differentiated thyroid cancer grows slowly in general, but some patients have recurrence and progress finally to death. To assess the difference in prognosis and establish appropriate thyroid surgery, Kobayashi *et al.*[12] studied 105 patients with differentiated thyroid cancer who were treated by total or subtotal thyroidectomy (excluding those with small tumours) under uniform conditions with respect to surgery. There were 77 women and 28 men aged 19–76 (mean 55) years. More than 60 per cent (alive) were followed for over 10 years. Thirty-eight patients (36 per cent) had recurrence. There were 19 deaths. Twelve of 31 patients with locoregional recurrence died and seven of these 12 died from locoregional control (neck and mediastinum). Age at first operation, tumour size and local tumour extension increased the rate of recurrence significantly. Multivariate analysis confirmed that age, locoregional recurrence and distant metastasis significantly affected survival. Although lymph node metastasis was not a prognostic factor, for patients at high risk of recurrence who are older and have large tumours with invasion, complete resection of cervical lymph nodes is advised to prevent local recurrence and prolong the disease-free interval. Prolongation of disease-free interval may lead to prolonged survival.

To investigate the growth mechanisms of thyroid tumours, the authors examined apoptotic cells in 61 thyroid tumours, consisting of 14 adenomas, 35 papillary carcinomas, four follicular carcinomas and eight undifferentiated carcinomas, using terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate digoxigenin-nick end labelling (TUNEL)[13]. The proliferative activity was also evaluated immunohistochemically using the monoclonal antibody to Ki-67 antigen (MIB-1) in the same tumours. The apoptotic index (AI) was expressed as the percentage of TUNEL-positive cells in the tumours, and a proliferation index (PI; the percentage of Ki-67-positive cells) was calculated for each tumour. The overall level of AI was very low in all histotypes of the thyroid tumours analysed; the mean AI was 0·5 in adenoma, 0·4 in differentiated carcinoma and 1·8 in undifferentiated carcinoma. The mean PI in thyroid tumour subtypes was significantly lower in adenoma and differentiated carcinoma, at 0·5 and 1·1 respectively, compared with 14·5 in undifferentiated carcinoma. There was no correlation between clinicopathological factors and AI or PI in differentiated thyroid carcinoma. These results suggest that apoptosis occurs infrequently in thyroid tumours and that proliferative activity markedly differs according to the thyroid tumour subtype. Moreover, the ratio between proliferating cells and apoptotic cells may reflect thyroid tumour progression.

General surgery

It is well known that zinc, an essential trace element, plays a role in wound healing[14]. Although the importance of zinc supplementation in total parenteral nutrition (TPN) has been recognized, the difference in tissue zinc distribution induced by TPN and whether this difference influences local wound healing remain uncertain. A study was conducted using 30 Sprague–Dawley rats to investigate the influence of TPN-induced changes in tissue zinc distribution on wound healing at intestinal anastomoses, and at muscle and skin suture sites. In the ordinary diet group, no significant differences were observed between subgroups with and without supplemental zinc in tissue zinc distribution or in the healing of intestinal, muscular and cutaneous wounds. In the subgroup given a low-protein diet without supplemental zinc, a gross change in tissue zinc distribution was noted to occur, with a concomitant marked decrease in zinc concentration and the tensile strength of healing wounds. These results indicate an association between wound healing and zinc concentration in the tissues examined in TPN-induced zinc deficiency with alternations in tissue zinc distribution. They also provide evidence of the local action of zinc in wound healing.

The development of postoperative intraperitoneal adhesions continues to be of major concern to surgeons[15]. The purpose of this study was to establish a postoperative adhesion model in rats, and to assess the effectiveness of tranilast (*N*-(3′,4′-dimethoxycinnamoyl) anthranilic acid) in preventing postoperative adhesion formation. The adhesion model was established in 12 male Donryu rats. This involved two essential factors, drying and bleeding. A further 22 male Donryu rats were used to study the prevention of intraperitoneal adhesions. Tranilast was administered orally before and after operation. Adhesion strength was evaluated by grading, and basic fibroblast growth factor (bFGF) and transforming growth factor (TGF) β1 concentrations were measured. Postoperative intraperitoneal adhesions were noted in all rats, but there were significantly fewer adhesions in the tranilast group than in the control group. Serum bFGF and TGF-β1 levels in the tranilast group were lower at the time of surgery than those in the control group, and bFGF levels were lower at the endpoint of the study in the tranilast group than in the control group. The TGF-β1 levels at the endpoint did not differ between the two groups. These findings demonstrate that tranilast significantly reduces postoperative intraperitoneal adhesion formation in rats.

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Editor-in-Chief
Surgery Today (The Japanese Journal of Surgery)

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Randomized clinical trial of early laparoscopy in the management of acute non-specific abdominal pain

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Background: Abdominal pain of uncertain aetiology (non-specific abdominal pain; NSAP) is the commonest reason for emergency surgical admission. The aim of this study was to examine the role of early laparoscopy in the management of NSAP.
Methods: Some 120 patients, admitted between November 1995 and October 1998 with acute abdominal pain of uncertain aetiology, were randomized into two groups: group 1 had laparoscopy during the first 18 h of admission and group 2 had close observation, conventional investigation and surgical intervention if signs of peritonism developed. Outcome measures were diagnosis, operative procedures, duration of hospital stay, readmission rate, morbidity and death, patient satisfaction and total number of investigations performed.
Results: Median hospital stay was 2 (range 1–13) days in both groups ($P = 0.87$). A diagnosis was established in 48 (81 per cent) of 59 patients in group 1 compared with 22 (36 per cent) of 61 in group 2 ($P < 0.0001$). The morbidity rate was 14 (24 per cent) of 59 in group 1 and 19 (31 per cent) of 61 in group 2 ($P = 0.3629$). The readmission rate at a median follow-up of 21 (range 1–35) months was 17 (29 per cent) of 59 in group 1 compared with 20 (33 per cent) of 61 in group 2 ($P = 0.6375$). Well-being scores improved from 134 on admission to 149 of 177 6 weeks later in group 1 ($P = 0.007$) and from 132 to 143 of 177 in group 2 ($P = 0.089$).
Conclusion: Early laparoscopy provided a higher diagnostic accuracy and improved quality of life in patients with NSAP.

Paper accepted 6 June 1999

British Journal of Surgery 1999, 86, 1383–1386

Introduction

Emergency admissions make up a large proportion of the overall general surgical workload. Incorporation of laparoscopy may improve the management of emergency admissions and also have important cost benefits, by reducing hospital stay and readmission rates[1–4]. The mean hospital stay for patients admitted with non-specific abdominal pain (NSAP) ranges between 4·1 and 6 days[4], using the traditional 'wait and see' management. This includes repeated clinical examination, radiological investigation[5] and a gynaecological opinion. A delay in surgical intervention while further investigations are performed may increase morbidity and prolong hospital stay. The end result may be an unsatisfactory discharge from hospital after a stay of 4–6 days, with a diagnosis of NSAP by exclusion.

If a definite diagnosis of NSAP could be made earlier and patients discharged, this could reduce costs[6]. A normal laparoscopy may allow the surgeon to discharge patients who are still symptomatic, confident that there is no requirement for laparotomy[1]. This may also reduce readmission rates for the same problem. Laparoscopy within 18 h of admission may therefore improve the outcome of patients admitted with acute NSAP. This study was a prospective randomized trial comparing early laparoscopy with the more traditional active observation.

Patients and methods

Patients were eligible for the trial if they had been admitted with acute abdominal pain of less than 7 days' duration and, after examination and baseline investigations had been performed, the diagnosis remained uncertain. After informed consent had been given, patients filled in a self-administered well-being questionnaire[7] and were randomized by sealed envelopes to either early laparoscopy or active observation and non-invasive investigation.

All patients who required acute surgical intervention on the basis of the history, clinical examination and investigations were excluded even if the exact diagnosis was uncertain. Baseline investigations included a full blood count, measurement of urea, electrolytes and serum amylase, urine culture, a pregnancy test in women of reproductive age, and a chest or abdominal radiograph if indicated clinically.

Quality of life

Gastrointestinal and general well-being was assessed on admission and after 6 weeks' follow-up by means of a combined Gastrointestinal Symptom Rating Scale (GSRS)[7] and Psychological General Well-Being Index (PGWB)[8]. The GSRS includes 15 questions about gastrointestinal symptoms divided into four degrees of severity for each question, giving a maximum score of 45. The PGWB addresses both positive and negative aspects of life and includes 22 questions divided into six dimensions: anxiety, depressed mood, positive well-being, self-control, general health and vitality. The combined maximum score is 177.

Laparoscopy

The patients randomized to early laparoscopy underwent surgery within 18 (median 10, range 2–39) h. Laparoscopy was performed using an open Hasson technique for the first port placement in the umbilical area with one 5-mm port in the midline suprapubic area and a third port if necessary. When no abnormality was identified at laparoscopy, appendicectomy was performed on the basis that symptoms caused by appendicitis are not always obvious at laparoscopy.

Statistical analysis

Data were analysed using Mann–Whitney *U* test or χ^2 test as appropriate. $P < 0{\cdot}05$ was considered statistically significant.

Results

Between November 1995 and October 1998, 120 patients admitted with NSAP (91 women) of median age 29 (range 16–84) years were randomized to either early laparoscopy or active observation and non-invasive investigation. A total of 146 eligible patients were approached and 26 refused to enter the study. This was either because they refused any surgery or because they insisted on early laparoscopy.

The age, sex, weight and white cell count in the two groups were comparable (*Table 1*). Radiological investigations undertaken in the two groups are shown in *Table 2*.

Table 1 Characteristics of patients with non-specific abdominal pain

	Early laparoscopy	Observation
Age (years)*	28 (16–84)	29 (16–62)
Sex ratio (M : F)	43 : 16	48 : 13
Weight (kg)*	64 (43–115)	68 (46–134)
White cell count ($\times 10^6$ per litre)*	11 000 (5300–23 100)	10 700 (3300–25 600)

*Values are median (range)

Table 2 Radiological investigations and referrals in patients with non-specific abdominal pain

	Early laparoscopy	Observation
Abdominal ultrasonography	4	34
Plain abdominal radiography	11	17
Chest radiography	5	5
Intravenous urography	0	1
Abdominal computed tomography	0	2
Gynaecological referral	2	8

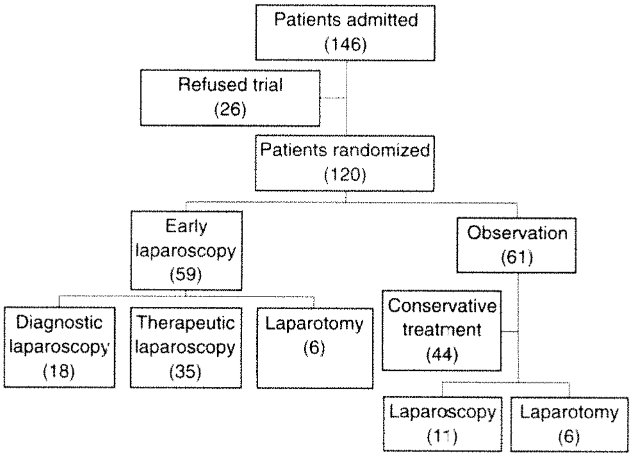

Fig. 1 Outcome of patients with non-specific abdominal pain

Eleven patients in the laparoscopy group underwent a total of 20 radiological investigations compared with a total of 59 investigations in 35 patients in the observation group ($P = 0{\cdot}0003$, χ^2 test).

The outcome of the two groups is summarized in *Fig. 1*. Seventeen patients (28 per cent) in the observation group required operative intervention owing to worsening symptoms or peritonitis. This occurred a median of 39 (range 15–119) h after admission. Surgery was performed laparoscopically in 11 of 17 patients. The final diagnosis in both groups is shown in *Table 3*. In the observation group 39 (64

Table 3 Final diagnosis in patients admitted with non-specific abdominal pain

Diagnosis	Early laparoscopy	Observation
Appendicitis*	23	8
Non-specific abdominal pain	11	39
Gynaecological pathology		
Ovarian cyst	6	3
Pelvic inflammatory disease	2	4
Ovarian tumour	2	2
Endometriosis	2	1
Retrograde menstruation	2	1
Fibroid uterus	1	0
Caecal diverticulitis/diverticular abscess	3	0
Caecal adenocarcinoma	1	0
Crohn's disease†	1	0
Torsion epiploica appendicularis‡	1	0
Omental torsion	1	0
Cholecystitis	1	0
Constipation	0	1
Gastroenteritis	0	1
Adhesions	2	1

*Histologically confirmed acute appendicitis; †diagnosed on appendix specimen; ‡torsion of appendix epiploica appendicularis with a normal appendix

per cent) of 61 patients remained without a clear diagnosis compared with 11 (19 per cent) of 59 in the early laparoscopy group ($P < 0{\cdot}0001$).

The duration of hospital stay was 2 (range 1–13) days in each group ($P = 0{\cdot}87$). Complications occurred in 14 (24 per cent) of 59 patients following early laparoscopy. These included abdominal pain that persisted for at least 1 month after discharge (seven patients), wound infection (five), wound dehiscence after laparotomy (one), and readmission with respiratory symptoms and shoulder tip pain (one). Complications occurred in 19 (31 per cent) of 61 patients after initial observation, and included abdominal pain persisting for at least 1 month in 15 patients and wound infection in four ($P = 0{\cdot}3629$). One patient in each group died. One patient in the observation group died at home, 7 days after discharge from a presumed pulmonary embolism. A second patient, in the early laparoscopy group, died from a massive pulmonary embolus 5 days after laparotomy despite full thromboprophylaxis.

Median well-being score on admission was 134 (range 58–171) in group 1 compared with 132 (range 93–169) in group 2. At 6 weeks after discharge, the well-being score had improved to 149 (range 84–173) in group 1 ($P = 0{\cdot}007$, Mann–Whitney U test) compared with 143 (range 88–167) in group 2 ($P = 0{\cdot}089$). These scores were based on a response rate to the second questionnaire of 80 per cent for group 1 and 74 per cent for group 2.

Seventeen patients in group 1 required readmission (total readmission 73 days) compared with 20 patients in group 2 who stayed a total of 105 days ($P = 0{\cdot}6375$). Three patients in the early laparoscopy group needed readmission as a direct consequence of the first admission. One patient was readmitted with respiratory symptoms and shoulder tip pain and was thought to have had a pulmonary embolus, although this could not be confirmed on a ventilation–perfusion scan. A second patient needed incision and drainage of an abscess at the site of the umbilical port. A third patient was admitted with recurrent appendicitis 9 months after laparoscopic appendicectomy. Stump appendicitis was diagnosed at laparotomy. This was the result of inflammation between two endoloops placed 1 cm apart at the base of the appendix[9].

Discussion

NSAP is a significant problem in general surgery and accounts for an estimated 13–40 per cent of all emergency surgical admissions. This prospective randomized trial has shown that early laparoscopy results in a higher diagnostic rate and significantly improved patient well-being 6 weeks after admission. There was, however, no significant improvement in morbidity and mortality rates, duration of hospital stay or readmission rates.

Laparoscopy within 18 h produced an overall final diagnosis rate of 81 per cent of cases. This is comparable to a reported rate of 77 per cent of cases when laparoscopy was used selectively and contrasts with a rate of less than 60 per cent without the use of laparoscopy[4]. An early definitive diagnosis made by laparoscopy was often valuable; laparotomy was often avoided, patients were reassured and appropriate treatment was started. Emergency laparoscopy was particularly useful in young women of child-bearing age who have a wider differential diagnosis for intraperitoneal inflammation[4,10–12]. Without laparoscopy the overall rate of unnecessary appendicectomy in women is reported to be approximately 39 per cent compared with 15 per cent in men[4]. Although a smaller number of men presented with NSAP in the present study, early laparoscopy proved to be valuable as a cause for the pain was found in all but two of the 16 men treated.

Early laparoscopy also has the benefit that a number of therapeutic options are available[13]. In this study, diagnostic laparoscopy became therapeutic in 35 (59 per cent) of the 59 patients randomized to early laparoscopy. Ovarian cysts can be drained and an ovarian torsion treated with immediate relief of symptoms. Purulent fluid collections secondary to pelvic inflammatory disease (PID) or diverticulitis can be drained[2]. Early recognition of PID enables early treatment.

which is important if complications such as infertility are to be minimized[4]. Women with undiagnosed endometriosis may benefit from early diagnosis[14]. An inflamed appendix can be removed safely and effectively laparoscopically[1,15,16]. Laparoscopic adhesiolysis is possible[17].

Significantly more patients underwent appendicectomy for acute appendicitis in the early laparoscopy group than in the observation group (23 *versus* eight; $P<0{\cdot}01$, χ^2 test). A number of patients in the observation group may have had early appendicitis which resolved with antibiotics[18]. A total of 26 appendicectomies were performed where the surgeon described the external appearance of the appendix at laparoscopy as normal. The policy was to remove the appendix during laparoscopy if no other clear cause of pain was found. This approach was adopted as previous authors have found external inspection of the appendix at laparoscopy to be an unreliable guide to the presence of appendicitis[19]. Of 26 appendices that looked normal externally in the present study, nine had significant pathological abnormalities on histological examination. Two specimens showed acute inflammation, another two contained parasites (*Enterobius* or *Oxyuris vermicularis*) and five had fibrous obliteration of the lumen or signs of chronic inflammation. The remaining 17 appendices were histologically normal.

De Dombal *et al.*[20] have reported that 10 per cent of patients aged over 50 years who presented with NSAP later developed gastrointestinal malignancy. One patient among the seven over 50 years of age was found to have a caecal carcinoma. An ovarian teratoma containing squamous carcinoma was diagnosed in a patient in the observation group 10 months following admission for NSAP in the present study.

Early laparoscopy is valuable in the management of NSAP; it provides a significantly higher diagnostic accuracy and a better improvement in quality of life than the more traditional approach of active observation.

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Original article

Electronic evaluation of the value of double gloving

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Background: Breakdown of the surgeon–patient barrier represents a risk for transmission of infectious disease. Such breakdowns are frequently not recognized by the surgical team. The protection afforded by double gloving under normal operating conditions was evaluated.

Methods: An electronic device detected breakdown of the surgeon–patient barrier in a series of 80 surgical procedures, randomly assigned to either double or single gloving. Fluid contact due to glove perforation, porosity or gown wetting was recorded during 151 individual surgeon episodes covering 238 operator-hours. Surgical procedures were called superficial for incisions of less than 10 cm.

Results: Double gloving reduced the number of perforation and porosity alarms twofold in both superficial and deep surgical procedures. Deep procedures carried a sevenfold increased risk of barrier breakdown compared with superficial procedures, the risk being greatest for the principal operator.

Conclusion: Without electronic detection, a large majority of barrier breakdowns would remain undetected by the surgical team and lead to prolonged contact with potentially contaminating body fluids. The use of double gloving provides real protection against such contamination risks.

Paper accepted 30 June 1999

British Journal of Surgery 1999, 86, 1387–1390

Introduction

Use of sterile impermeable gloves and surgical gowns to provide a sterile barrier between surgeon and patient is a key concept in modern surgical practice. Breakdown of this barrier is thought to be infrequent[1,2]; however, recent studies have indicated a high frequency of barrier breakdown leading to potentially contaminating contact between surgeon and body fluid during operation[3,4]. Latex gloves and dry gowns are electrically resistant, thus continuous measurement of resistance between the surgeon's skin and the patient provides an independent measure of barrier failure[5,6]. The Elper (Sofracob, Vienne, France) apparatus generates a signal between electrodes placed on the patient and individual members of the surgical team[3]. An abrupt change in electrical resistance may indicate penetration of a glove or rapid soaking of a gown, whereas a more gradual change is associated with development of glove porosity[7], which may be sufficient to permit passage of viruses[8]. In the absence of a painful stimulus, even visible glove holes may not be perceived by the operator, thus potentially contaminating contact may persist until the end of the operation. Double gloving and use of reinforced gowns are often recommended to reduce the risk of contamination[9,10].

This study examined the value of the Elper apparatus in detection of sterile barrier breakdown between patients and surgeons during operations in which surgeons were randomly assigned to single or double gloving.

Patients and methods

All surgical procedures performed in the morning session at the Lyon-Sud Hospital (Surgical Emergency Service) from February 1996 to April 1996 were monitored after being randomly assigned to double or single gloving (Triflex; Baxter, Maurepas, France). The surgical team wore paper gowns (Mölnlycke, Linselles, France). One session was excluded from the randomly assigned series because the patient was known to be infected with human immunodeficiency virus (HIV); however, patients' serological status for HIV was not determined systematically. The surgical procedures were classified into two categories for risk evaluation. Deep surgical procedures involved abdominal incisions of at least 10 cm allowing palpation of the viscera ($n = 33$), while superficial surgical procedures did not ($n = 47$). Laparoscopic procedures were considered as superficial for the purposes of the study.

All signals (alarms) from the Elper apparatus were logged and their cause determined immediately. Abrupt signals were confirmed by visual inspection of gloves for holes or tears. Small holes were detected by filling the suspect glove with water and observing leaks. Damaged or porous gloves or wet gowns were changed immediately. The observer did not participate in the operating procedure. Recorded information included the type of gloving, the nature and time of each alarm, the member of the team involved and the total operating time. Together with the operating records, this allowed determination of the frequency of barrier breakdown for the types of operation, the members of the team and the protective precautions used.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA) software on a personal computer. Results are expressed, where appropriate, as relative risk with 95 per cent confidence interval (c.i.). The Mann–Whitney *U* test or analysis of variance (ANOVA) was used to compare several means and the χ^2 test to compare percentages where appropriate.

Results

One hundred and sixty-four alarms (31 glove perforations, 25 glove porosity, 32 mixed glove porosity and perforation, and 76 wet gowns) were recorded during 80 surgical procedures on 56 half-days, resulting in 151 exposures (involvement of individual surgical team members) during 238 operator-hours. Deep surgical procedures accounted for 61 exposures and superficial procedures for 90 (*Table 1*). The mean(s.d.) duration of operation was significantly greater for deep than for superficial procedures (2·1(1·2) *versus* 1·2(0·8) h; $P < 0{\cdot}001$).

Alarms were more frequent during deep surgical procedures. At least one alarm occurred during 78 per cent (45 of 61) of exposures for deep procedures, compared with only 24 per cent (22 of 90) for superficial procedures (relative risk 3·0 (95 per cent c.i. 2·0–4·5)). Deep procedures generated 137 alarms compared with only 27 during superficial procedures ($P < 0{\cdot}001$, χ^2 test). Porosity alarms were observed only during deep procedures. The principal operator was implicated in 120 alarms of which 72 concerned gloving failure, whereas the assistant was implicated in 44 alarms of which 16 concerned gloving failure (relative risk 1·3 (95 per cent c.i. 1·0–1·7)).

In the present series the Elper apparatus detected 31 of 32 glove perforations confirmed by postoperative testing of used gloves, corresponding to a specificity of 97 per cent. Based on visual inspection, the negative predictive value was 99·6 per cent for all incidents.

Double gloving reduced the number of alarms in all circumstances. Single gloves were worn in 74 exposures, during 48 of which a total of 116 alarms occurred. Double gloves were worn in 77 exposures during 25 of which a total of 48 alarms occurred. The protective effect of double gloving on the number of alarms was significant ($P < 0{\cdot}001$, ANOVA). Deep surgical procedures resulted in seven times the mean number of alarms compared with superficial surgical procedures. In both cases the use of double gloves reduced the incidence of alarms by half.

Table 1 Distribution of individual exposures during surgical procedures

	Procedures (n=80)	Exposures (n=151)
Deep procedure		
Small bowel or colorectal surgery	17	30
Major hernia repair	6	11
Biliary, gastric or splenic surgery	8	16
Gynaecological surgery	2	4
Superficial procedure		
Minor hernia repair	17	34
Laparoscopy	15	29
Proctology or venous surgery	6	12
Appendicectomy	5	10
Minor procedure	4	5

Table 2 Calculated time of inadvertent fluid contact due to unrecognized barrier breakdown

	Inadvertent contact (h)	No. of alarm-free hours	Inadvertent contact per 100 h	P*
Gloving				
Single	69	60	53·5	<0·001
Double	32	77	29·4	
Surgery				
Deep	84	45	65·1	<0·001
Superficial	17	92	15·6	
Operator				
Principal	63	59	51·6	0·004
Assistant	38	78	32·8	

*Mantel–Haenszel χ^2 test

The operator recognized only six perforations immediately, although 31 Elper alarms indicated glove puncture, but never spontaneously recognized increased glove porosity. By recording the time at which the electronic alarm indicated barrier failure and the time at which the surgical procedure was completed, it was possible to determine the duration of inadvertent fluid contact that would have occurred in the absence of electronic detection. For 100 h of operating time, a member of the surgical team would have had inadvertent contact with patients' body fluids for a mean of 42 h. The principal operator would have been more exposed to fluids than the assistant. The duration of this inadvertent fluid contact would have been greater during deep surgery (65·1 h) than superficial surgery (15·6 h), and would have been clearly reduced by the use of double gloves (*Table 2*).

Discussion

The use of double gloving has often been recommended as a reinforcement of the surgeon–patient barrier, but the resulting benefit has rarely been tested using electronic real-time detection. Diminished tactile sensitivity is a common objection[11], and requires a real reduction in risk to justify introduction of double gloving. This study has shown that double gloving reduces the number of glove perforations and incidents of porosity that might result in contact with body fluids. The number of alarms due to glove failure was approximately halved by use of double gloving. This finding was confirmed by inspection of the gloves used during various procedures. Of 11 perforation alarms that occurred in the double-gloving group, all showed visible perforation of both layers, but ten glove pairs from operations during which no perforation alarm occurred showed damage to the outer glove alone.

Double gloving shows benefit in both deep and superficial operative procedures, and for both principal surgeons and their assistants. Most incidents causing alarms occur during deep surgical procedures and concern the principal operator, suggesting that precautions are particularly valuable in these situations. The findings confirm observations that only a minority of perforations are perceived by the operator. The six incidents reported to the observer represented 19 per cent of the 31 perforation alarms that were confirmed by glove inspection, or 7 per cent of all glove-related alarms (including porosity). This is in general agreement with the perception rate of 15 per cent reported by Macintyre *et al.*[3], also using the Elper apparatus. However, very small punctures may not be detected reliably; a similar electrical system reacted to six of 20 experimental glove punctures by a 9/0 surgical needle[12]. Failure to appreciate breakdown of the surgeon–patient barrier can lead to prolonged fluid contact, with consequent increased risk of transmission of viral or other pathogens[13]. This risk may operate in both directions, as shown by a recent report of contamination of a patient by a surgeon infected with HIV during an orthopaedic operation[14].

The reliability of the Elper apparatus seems excellent for perforations and gown wetting, which can be independently confirmed by inspection. Only rarely do perforations go undetected, probably because of dry conditions. Glove porosity is, however, hard to detect independently, and the number of false alarms for this parameter is impossible to assess accurately. In the absence of an alarm, there is a 99·6 per cent probability that no barrier breakdown detectable by independent inspection has occurred.

Double gloving appears to be a simple and effective means of risk reduction. If necessary, single gloves might be used for particularly delicate operations, with resumption of double gloves as soon as practical. The number of alarms due to wet gowns suggests that efficient reinforced gowns could make an appreciable contribution to maintenance of the surgeon–patient barrier. It would be desirable to generalize the use of electronic detectors such as the Elper apparatus to reduce the time of inadvertent contact between surgeon and patient and to facilitate immediate glove or gown change as required. Such protective procedures should not interfere with operating technique, or increase the time or cost of surgical interventions.

Acknowledgements

The authors thank Mr T. B. Greenland for help in preparing this article. Financial support was received from the Université Claude Bernard, Lyons, France.

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£100 000 Awarded for Surgical Research

With the award of another three research bursaries in 1999, the Council of the BJS has now donated £100 000 for surgical research in the past 3 years. This year, the successful winners of £10 000 were:

Ms B. Lovatt FRCS. Royal Free and University College Medical School, London, UK. Is the randomized controlled trial an appropriate tool for the assessment of surgical technique? A systematic review.

Ms C. L. McGuinness FRCS. St Thomas' Hospital, London, UK. MMP expression and activity in the aneurysm wall of patients treated with doxycycline.

Mr L. S. Wong MD FRCS. Warwick University and Walsgrave Hospital, Warwick, UK. Bone marrow tumour cells: evidence of residual disease or marker of metastatic disease in patients with colorectal cancer.

The standard of application from the 84 entrants (the largest number yet for BJS awards) for the 1999 awards was extremely high but, unfortunately, it was only possible to make three awards. All entrants have been offered the possibility of 'fast-track publication' of their work in the Journal when it is eventually completed. Full details of the awards and commended runners-up can be found on the BJS website: www.bjs.co.uk

It is hoped that further research bursaries will be available in the summer of 2000.

J. J. Earnshaw
Associate Editor

Original article

Hepatitis viral status in patients undergoing liver resection for hepatocellular carcinoma

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Background: Hepatitis B and C viruses are the main causative agents of hepatocellular carcinoma (HCC). The influence of hepatitis viral status on liver resection for HCC remains undetermined.
Methods: Patients who underwent curative resection for HCC were divided into four groups: group 1, seronegative for hepatitis B surface antigen (HBsAg) and antihepatitis C antibody (HCVAb); group 2, seropositive for HBsAg only; group 3, seropositive for HCVAb only; and group 4, seropositive for HBsAg and HCVAb. The clinicopathological characteristics and surgical results of the four groups were compared. Resection of HCC was determined according to liver functional reserve and tumour extent.
Results: There were 40, 131, 70 and 20 patients in groups 1, 2, 3 and 4 respectively. Due to patient selection bias, there were significant differences in some background features, resectional extent and pathological characteristics among the four groups. Postoperative morbidity and mortality, as well as the Union Internacional Contra la Cancrum tumour node metastasis stages, did not differ. Patients in group 1 had a higher disease-free survival rate than those in group 2 ($P = 0{\cdot}02$). The actuarial survival rates of patients in groups 2 and 4 were lower than those of groups 1 and 3.
Conclusion: With careful patient selection, the hepatitis viral status does not influence the surgical risks of hepatectomy for HCC. After liver resection for HCC, the long-term survival rate of patients seronegative for HBsAg is greater than that of patients seropositive for HBsAg.

Paper accepted 6 July 1999

British Journal of Surgery 1999, 86, 1391–1396

Introduction

As an endemic area for hepatitis B virus (HBV) infection, most patients with hepatocellular carcinoma (HCC) in Taiwan are seropositive for hepatitis B surface antigen (HBsAg)[1–9]. After the discovery of the hepatitis C virus (HCV) genome in 1989[1–3], both HBV and HCV have been claimed to be major causes of HCC[1–15]. Several studies from Taiwan have also revealed that seropositivity for antihepatitis C antibody (HCVAb) is frequently found in patients with HCC who are seronegative for HBsAg[5–7]. Nevertheless, some patients with HCC are doubly infected[6–8,10,12], whereas others are negative for both HBsAg and HCVAb[6–8,12,13].

Surgical resection remains the only curative option for HCC[8,9,11–18]; however, local recurrence in the liver is common[8,9,11–18]. Carcinogenicity of viral hepatitis in the remnant liver has been suggested as the cause of recurrence[1,2,4,9]. Because of different courses of cancer development[1–10], the characteristics of HBV- and HCV-related HCC are different[5–7,9,10], and long-term survival for HCC in patients with different hepatitis viral statuses may also differ[8,11–15]. In addition, only a few reports have simultaneously evaluated the results of resection in patients with different combinations of HBV and HCV infection[8,11–13].

To evaluate the influence of hepatitis viral status on liver resection for HCC, the clinicopathological features and outcome of patients undergoing resection for HCC, with different serological HBsAg and HCVAb statuses, were reviewed and compared.

Patients and methods

A retrospective review of patients undergoing curative hepatic resection for HCC between July 1990 and June 1997 was undertaken. In all patients, serum α-fetoprotein (AFP) level was measured, serum HBsAg and HCVAb concentrations were checked, and conventional liver function tests, indocyanine green (ICG) clearance test, and imaging studies (including abdominal ultrasonography, computed tomography and angiography) were performed. Couinaud's liver segmentation[19] was used to express tumour location and extent of hepatectomy.

If the patient agreed to surgery and their physical state fulfilled class I or II of the American Society of Anesthesiologists classification[18], regardless of hepatitis status, liver resection was determined according to tumour location and extension, preoperative liver function and ICG 15-min retention rate (ICG R15)[16–18]. In surgical patients with negative HBsAg, serum levels of hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb)[3,4] were checked.

According to seropositivity for HBsAg and HCVAb, patients were divided into four groups: patients seronegative for both HBsAg and HCVAb (group 1); patients seropositive for HBsAg only (group 2); patients seropositive for HCVAb only (group 3); and patients seropositive for both HBsAg and HCVAb (group 4).

Assays of hepatitis seromarkers were performed using commercially available radioimmunoassay kits (Abbott Laboratories, Chicago, Illinois, USA). Positivity for HCVAb was determined with the Abbott HCV kit, a second-generation enzyme-linked immunoassay (Abbott Laboratories).

Intraoperative ultrasonography was performed routinely to detect impalpable tumours[9,16–18]. Resected specimens were sent to senior pathologists (W.-L.H. and J.-T.C.) to determine the pathological characteristics and resection margins[16–18]. The largest tumour diameter was recorded as tumour size in cases of multiple tumours[17]. The Union Internacional Contra la Cancrum tumour node metastasis (UICC TNM) staging system[20] was applied to each patient after pathological confirmation.

Excluding postoperative deaths, all patients were followed at the outpatient clinic until March 1999. Serum AFP level was checked and abdominal ultrasonography performed every 3–4 months. Abdominal computed tomography was performed every 6 months. If tumour recurred in the remnant liver, patients underwent either repeat resection or transcatheter arterial chemoembolization[9,16–18]. For irresectable extrahepatic recurrences, systemic chemotherapy (cisplatin, 5-fluorouracil and epirubicin) was administered[16–18].

Statistical analysis

The clinicopathological features and operative results of the four groups were compared. Continuous variables are presented as the mean(s.e.m.). Comparisons between two groups were performed with the Mann–Whitney *U* test, and differences among groups were compared with Kruskal–Wallis one-way analysis of variance. Comparison of frequencies was performed with the Pearson χ^2 test or two-tailed Fisher's exact test.

The disease-free and actuarial survival rates were calculated by Kaplan–Meier life-table methods and compared with a generalized Wilcoxon test. Differences were considered to be significant at $P \leq 0{\cdot}05$. All statistical analyses were performed by means of commercially available computer software (SPSS/PC+; SPSS, Chicago, Illinois, USA).

Results

A total of 1035 patients with HCC was admitted. The number of patients resected in each group was: group 1, 40 (27 per cent) of 149; group 2, 131 (24 per cent) of 556; group 3, 70 (28 per cent) of 252; and group 4, 20 (26 per cent) of 78 ($\chi^2 = 1{\cdot}97$, 3 d.f., $P = 0{\cdot}58$). Of patients in group 1, 36 were positive for HBsAb, 31 were positive for HBcAb, and only two were negative for HBsAb and HBcAb. Similarly, among those in group 3, 45 were positive for HBsAb, 32 were

Table 1 Background characteristics of the resected patients with hepatocellular carcinoma

	Group 1 (*n*=40)	Group 2 (*n*=131)	Group 3 (*n*=70)	Group 4 (*n*=20)	*P*
Mean(s.e.m.) age (years)	68·9(1·9)	54·3(1·1)†	64·1(1·1)	53·0(2·5)‡§	<0·0001*
Sex ratio (M : F)	29 : 11	110 : 21	56 : 14	16 : 4	0·45
Asymptomatic patients	3	23	11	2	0·26
Associated cirrhosis	24	102¶	58**	17	0·03
AFP ≥ 200 ng/ml	10	56	13††	5	0·003*
Mean(s.e.m.) ICG R15 (%)	13·7(0·8)	12·9(0·5)	17·3(0·9)††,§§	16·6(1·5)¶¶	0·0001*
Mean(s.e.m.) tumour size (cm)	5·9(0·7)	7·4(0·5)‡	5·0(0·4)	6·7(1·0)	0·007*
Multiple tumour (≥ 2)	5	23	14	4	0·84

AFP, α-fetoprotein; ICG R15, indocyanine green 15-min retention rate. *Kruskal–Wallis one way analysis of variance among the four groups; †$P < 0{\cdot}0001$ *versus* groups 1 and 3, ‡$P = 0{\cdot}0007$ *versus* group 3, §$P = 0{\cdot}0002$ *versus* group 1, ¶$P = 0{\cdot}04$ *versus* group 1, **$P = 0{\cdot}01$ *versus* group 1, ††$P < 0{\cdot}0001$ *versus* group 2, §§$P = 0{\cdot}01$ *versus* group 1, ¶¶$P < 0{\cdot}02$ *versus* group 2 (Mann–Whitney *U* test)

Table 2 Operative procedures and intraoperative results

	Group 1 (n=40)	Group 2 (n=131)	Group 3 (n=70)	Group 4 (n=20)	P
Extent of liver resection					
⩾3 segments	10	50	14†	4	0·03
2 segments	11	33	16†	9	
⩽1 segment	19	48	40†	7	
Concomitant procedures	5	25	6	4	0·22
Resection of diaphragm	4	14	4	3	
Adrenectomy	0	0	1	0	
Colectomy	1	2	0	0	
Gastrectomy	0	2	1	0	
Resection of common bile duct	1	1	0	1	
Partial resection of duodenum	0	1	0	0	
Partial resection of IVC	0	1	0	0	
Portal vein thrombectomy	0	5	0	0	
Mean(s.e.m.) operative blood loss (ml)	1155(213)	1563(138)	1257(125)‡	1629(294)§	0·03*
Mean(s.e.m.) blood transfused (ml)	403(121)	597(93)	364(75)	912(237)¶	0·05*

IVC, inferior vena cava. *Kruskal–Wallis one-way analysis of variance between the four groups; †P = 0·01 *versus* group 2, ‡P = 0·03 *versus* group 2, §P = 0·02 *versus* group 1, ¶P = 0·02 *versus* groups 1 and 3 (Mann–Whitney U test)

Table 3 Surgical morbidity and mortality of resected patients with hepatocellular carcinoma

	Group 1 (n=40)	Group 2 (n=131)	Group 3 (n=70)	Group 4 (n=20)	P†
Complications	5	23	13	4	0·84
Ascites	1	7	2	1	
Bile leakage	2	6	2	1	
Intra-abdominal abscess	1	5	1	1	
Urinary tract infection	2	2	2	2	
Pleural effusion	1	1	2	1	
Pneumonia	1	2	2	0	
Prolonged jaundice*	0	1	1	0	
Postoperative bleeding	0	1	1	0	
Wound infection	0	1	2	1	
Anaesthetic accident	0	1	0	1	
Myocardial infarction	1	0	0	0	
Bed sore	0	1	0	0	
Hypnotics overdose	0	1	0	0	
Parotitis	0	0	1	0	
Peptic ulcer perforation	1	0	0	0	
Deaths	1	3	0	1	0·47

*Defined as a prolonged increase in serum total bilirubin concentration (⩾ 7 mg/dl for 1 week). †Pearson's χ^2 test

Table 4 Pathological characteristics of resected specimens

	Group 1 (n=40)	Group 2 (n=131)	Group 3 (n=70)	Group 4 (n=20)	P
Mean(s.e.m.) resected liver weight (g)	254·5(42·3)	400·8(54·3)	176·5(26·4)†	334·6(115·7)	0·003*
Mean(s.e.m.) resection margin (mm)	7·0(1·3)	7·4(0·7)	4·9(0·9)‡	5·8(1·0)	0·03*
Microvascular involvement	8	43	13	5	0·12
Well formed capsule	16	37	29	7	0·23
Associated satellite nodules	13	60	18§	9	0·03
Edmondson–Steiner grade (I + II *versus* III + IV)	11 *versus* 29	23 *versus* 108	12 *versus* 58	4 *versus* 16	0·53
UICC TNM stage (I : II : III : IV)	4 : 14 : 14 : 8	6 : 40 : 40 : 45	6 : 25 : 27 : 12	0 : 7 : 9 : 4	0·23

UICC TNM, Union Internacional Contra la Cancrum tumour node metastasis. *Kruskal–Wallis one-way analysis of variance between the four groups: †P = 0·0003 *versus* group 2, ‡P = 0·009 *versus* group 2, §P = 0·006 *versus* group 2 (Mann–Whitney U test) positive for HBcAb and only five were negative for both HBsAb and HBcAb.

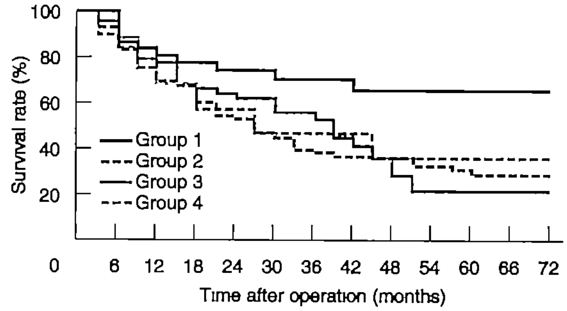
The background data for resected cases are shown in *Table 1*. There were statistically significant differences regarding age, incidence of cirrhosis, AFP level, ICG R15 and tumour size among the four groups. When comparisons were made between two groups, the age of patients negative for HBsAg (groups 1 and 3) was significantly greater than that of patients positive for HBsAg (groups 2 and 4). However, patients in group 1 had a lower incidence of associated cirrhosis. Patients with negative HCVAb status (groups 1 and 2) had a lower ICG R15 than those with positive HCVAb (groups 3 and 4). In group 2, the serum AFP level was higher and the tumour size was greater than in group 3.

The operative procedures are shown in *Table 2*. Because of different background features, the resectional extent, amount of operative blood loss and amount of blood transfused also differed. Postoperative complications (*Table 3*) occurred in 45 patients. Five patients (2 per cent) died after operation. There were no significant differences with respect to operative morbidity or mortality among the four groups.

The pathological characteristics and UICC TNM stages of HCC are shown in *Table 4*. The incidence of associated satellite nodules was higher in group 2 than in group 3. Because of lesser hepatectomy extent, the resected liver weight was smaller and the resection margin narrower in group 3 compared with group 2. Differences in UICC TNM stages among the four groups were not statistically significant.

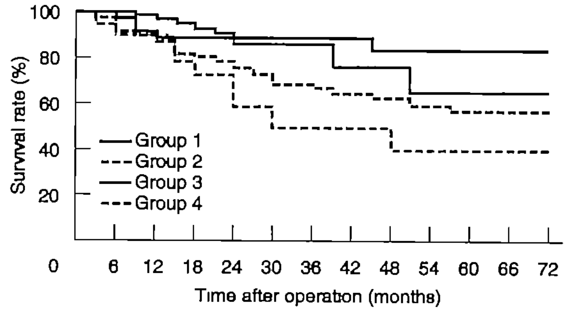
Long-term results

The median (range) follow-up time was 34·5 (4·1–104·5) months. Recurrent HCC has been noted in 11 patients in group 1, 69 in group 2, 32 in group 3 and ten in group 4. The 5-year disease-free survival rate of groups 1, 2, 3 and 4 was 66, 29, 22 and 36 per cent respectively (*Fig. 1*). Differences among the four groups were not statistically significant. However, patients in group 1 had a significantly higher disease-free survival rate than those in group 2, $P = 0{\cdot}02$ (group 1 *versus* group 2 (generalized Wilcoxon test). Reoperation for recurrent cancer was possible in three patients in group 1, 19 in group 2, 14 in group 3 and one in group 4. Including four patients who died without cancer recurrence (two each in groups 2 and 3), the 5-year actuarial survival rate of groups 1, 2, 3 and 4 was 83, 57, 65 and 40 per cent respectively (*Fig. 2*). Differences among the four groups were significant ($P = 0{\cdot}01$). Moreover, patients in groups 1 and 3 had a significantly higher survival rate than those in groups 2 and 4, $P = 0{\cdot}05$ (group 1 *versus* group 2), $P = 0{\cdot}02$ (group 1 *versus* group 4), $P = 0{\cdot}02$ (group 2 *versus* group 3), $P = 0{\cdot}006$ (group 3 *versus* group 4) (generalized Wilcoxon test).



No. at risk							
Group 1	39	27	22	16	13	7	4
Group 2	128	74	48	26	19	12	7
Group 3	70	43	25	15	4	2	2
Group 4	19	13	6	4	3	3	2

Fig. 1 Disease-free survival rates of patients with resected hepatocellular carcinoma according to hepatitis status.
Group 1, seronegative for both hepatitis B surface antigen (HBsAg) and antihepatitis C antibody (HCVAb);
Group 2, seropositive for HBsAg only;
Group 3, seropositive for HCVAb only;
Group 4, seropositive for both HBsAg and HCVAb



No. at risk							
Group 1	39	29	25	19	15	8	4
Group 2	128	91	68	47	36	22	12
Group 3	70	53	33	18	7	4	3
Group 4	19	17	7	5	4	4	3

Fig. 2 Actuarial survival rates of patients with resected hepatocellular carcinoma according to hepatitis status.
Group 1, seronegative for both hepatitis B surface antigen (HBsAg) and antihepatitis C antibody (HCVAb);
Group 2, seropositive for HBsAg only;
Group 3, seropositive for HCVAb only;
Group 4, seropositive for both HBsAg and HCVAb

Discussion

Active viral hepatitis B and C infection, through a sequence of chronic hepatitis and liver cirrhosis, is the most common cause of HCC oncogenesis[1–7,9,10]. To determine the presence of active hepatitis infection, it is best to include checks for serum HBV DNA and HCV RNA[1–3]. However, testing both components by a polymerase chain reaction method is complicated, time-consuming and expensive[1–3], and is rarely used to screen the general population[2]. Because of the high accuracy of checking serum HBsAg and HCVAb for active viral infection[1–3], commercially available kits, similar to those in previous reports[4–15], were used to determine the hepatitis viral status of patients with HCC in this study.

As an HBV endemic area, most people in Taiwan have a history of asymptomatic HBV infection[3–7]. Only 5·6 per cent of the general population is seronegative for all three HBV markers (HBsAg, HBsAb and HBcAb)[4]. For HCC cases, the incidence is even lower[7]. Only two surgical patients in this study were seronegative for all hepatitis markers. The proportions of HBsAg and HCVAb status among the admitted or resected patients with HCC were similar to those of other reports from Taiwan regarding HCC populations[3–7].

The reported clinicopathological features of resected patients with HCC and different hepatitis status have not been consistent[8,11–15]. These inconsistencies may be related to different patient selection criteria because the total number of patients admitted with HCC and resectability in those with differing viral status were not mentioned[8,11–15]. Moreover, the numbers of patients seronegative for both HBsAg and HCVAb in these studies were low, or even non-existent[8,11–15].

Resectability of HCC is usually decided by the number of patient referrals, general condition of the patients, liver functional reserve and tumour extension[2,9,17]. Moreover, because many non-operative modalities have been proposed for HCC[9], the surgeon's attitude toward liver resection, especially in octogenarians[18], patients with impaired liver function[16] or those with bilobar disease[17], may affect resectability. The present authors' resection rate was low even with an aggressive strategy for HCC resection, but is comparable to that in previous studies[8,11–15]. The resection rate among the four serological status groups was not different, allowing the influence of hepatitis viral status on the results of surgically treated patients with HCC to be investigated.

HBV and HCV spread via different routes[1–10]. HBsAg-positive patients with HCC are usually younger with better liver function reserve and higher AFP level than HBsAg-negative patients with HCC[1–10,18]. On the other hand, those with HCC without active hepatitis infection (group 1) had a lower incidence of associated cirrhosis[9,13]. In this study, patient selection for liver resection was based on case-by-case differences in general condition and liver function. In spite of different background features, surgical morbidity and mortality did not differ among the four groups.

Long-term results of hepatectomy for patients with HCC with different hepatitis viral status are inconsistent[8,11–15]. Most authors have claimed that long-term prognosis is not influenced by hepatitis viral status[8,11,13,15]. However, Yamanaka *et al.*[12] reported that patients with non-B, non-C-related HCC have a higher disease-free survival rate than those with HCV-related HCC. Haratake *et al.*[14] reported that HCVAb-positive patients with HCC have a higher long-term survival rate than HBsAg-positive patients with HCC. The reported factors affecting HCC prognosis were age[2,18], AFP level[2,3,9], associated cirrhosis[2,9], tumour size[2,9], tumour number[2,14], presence of vascular invasion and/or satellite nodules[2,9,14], and cancer stage[9,12,14]. In this series, UICC TNM stages did not differ among the four groups. However, because a higher incidence of poor prognostic features was found in the presence of HBsAg, patients in groups 2 and 4 had a lower survival rate.

Based on the results of this study, hepatitis viral status does not influence the operative risk of hepatectomy for HCC; however, HBsAg-positive patients have a poorer outcome after liver resection than HBsAg-negative patients.

Acknowledgements

The authors thank Professor M. Makuuchi, Second Department of Surgery, Faculty of Medicine, Tokyo University, Tokyo, Japan, for suggestions regarding this manuscript and Ms F. L. Kuo for statistical assistance.

This work was supported in part by research grant no. NSC 88-2314-B-075A-012 from the National Science Council, Republic of China.

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Original article

Laparoscopy extends the indications for liver resection in patients with cirrhosis

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Background: Clinical or biological evidence of liver failure is usually considered a contraindication to open liver surgery as it is associated with a prohibitive risk of postoperative death.

Methods: This report describes three patients who had resection of a superficial hepatocellular carcinoma suspected either to be ruptured, or at high risk of rupture, using the laparoscopic approach. All three patients had intractable ascites, in two superimposed on active hepatitis. Surgery was performed under continuous carbon dioxide pneumoperitoneum with intermittent clamping of the hepatic pedicle.

Results: Intraoperative blood loss was between 100 and 400 ml; no blood transfusion was required. The postoperative course was uneventful except for a transient leak of ascites through the trocar wounds. Duration of in-hospital stay was 6–10 days. Liver function tests had returned to preoperative values within 1 month of surgery in all patients.

Conclusion: The laparoscopic approach may enable liver resection in patients with cirrhosis and evidence of liver failure that would contraindicate open surgery.

Paper accepted 11 July 1999

British Journal of Surgery 1999, **86**, 1397–1400

Introduction

The incidence of spontaneous rupture of a hepatocellular carcinoma (HCC) is estimated to range between 5 and 15 per cent[1–3]. Rupture does not always result in massive bleeding and in up to one-third of patients presents only as haemorrhagic ascites[1,4]. Without treatment, ruptured HCC is associated with a 1-month mortality rate of 90 per cent and no 1-year survivors[4]. If, however, bleeding is controlled and the tumour resected, the 1-month mortality rate is 27 per cent[4] and the 3-year survival rate may be as high as 41 per cent[5,6]. Long-term survival of up to 9 years has been reported[7].

An active approach to the management of ruptured HCC is hampered by the usual association with decompensated liver cirrhosis that precludes conventional surgical resection. Some 80 per cent of patients with a ruptured HCC have underlying cirrhosis[8] and 78 per cent of patients with cirrhosis are Child's grade B or C[9] at the time of diagnosis. Resection at that stage has, in the past, been almost invariably fatal[9,10]. Hence, most ruptured HCCs are treated by chemoembolization, hepatic artery ligation or plication. These measures are fairly effective in controlling bleeding but do not offer a chance for medium- or long-term survival[4].

One way to avoid being faced with such a situation is to remove superficial HCCs with an outward protrusion, as this morphological feature is present in 88 per cent of ruptured HCCs[5]. Potential rupture is especially risky when associated with blood-stained ascites or sudden onset of epigastric pain. In the present study three patients with decompensated cirrhosis considered a contraindication to open surgery had laparoscopic liver resection.

Patients and methods

Patients

The first patient was a 56-year-old man with cirrhosis in whom a routine paracentesis for intractable ascites incidentally became bloodstained. The patient remained stable haemodynamically and had a normal haemoglobin level. Spiral computed tomography (CT) disclosed a 3·5-cm hypervascular HCC protruding from the surface of liver segment 7 (*Fig. 1*). The patient was malnourished and had a serum bilirubin level of twice the normal upper range and a

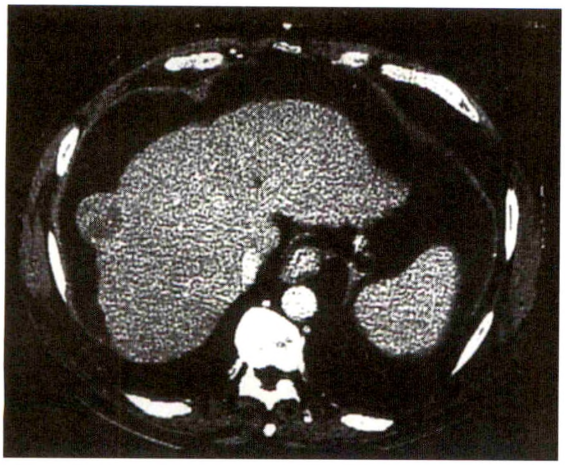

Fig. 1 Preoperative computed tomogram showing a hepatocellular carcinoma protruding from the surface of liver segment 7 with surrounding ascites

prothrombin time (expressed as a percentage of controls) of 69 per cent.

The second patient was a 59-year-old man with hepatitis C-related cirrhosis in whom routine ultrasonography revealed a 3-cm hypervascular HCC protruding from the anterosuperior surface of the junction between liver segments 2 and 4. He had intractable ascites, serum bilirubin and transaminase levels of 1·5 and three times the normal upper range respectively, a serum albumin level of 29 g/l and a prothrombin time of 47 per cent.

The third patient was a 62-year-old man with known hepatitis B-, hepatitis C- and alcohol-related cirrhosis who suddenly developed severe epigastric pain and a palpable tender epigastric mass. Spiral CT revealed a 4-cm hypervascular HCC protruding from liver segment 3 in the projection of the palpable epigastric mass. He had marked ascites, serum bilirubin, transaminase and γ glutamyl transpeptidase (GGT) levels of three, five and 30 times the normal upper range respectively, and a prothrombin time of 67 per cent.

Methods

All three patients underwent elective liver surgery. The surgeon was positioned between the patient's legs. Continuous carbon dioxide pneumoperitoneum was used at a pressure ranging between 10 and 15 mmHg. Five to six trocars were employed per patient. The hepatic pedicle was encircled with a tape passed in a 24-Fr rubber drain. Non-anatomical resection of the tumour with a 1-cm margin was performed using an ultrasonic dissector (Dissectron, Satelec, France) under two to three sessions of intermittent hepatic pedicle clamping of 15 mins' duration. Small vascular or biliary radicles were divided after bipolar coagulation, or between endoclips. The resected liver was removed into an endopouch via an enlarged periumbilical trocar incision. A suction drain was left in the peritoneal cavity and all abdominal incisions were closed using absorbable sutures.

Results

The duration of operation ranged between 2 and 3·5 h; no blood transfusion was required. Intraoperative and postoperative details are summarized in *Table 1*. The only complication, which occurred in every patient, was a persistent ascites leak after removal of the suction drain which required closure of the drain site. At the time of discharge, liver function tests had returned to preoperative values except in patient 3 who still had a raised serum bilirubin at six times the normal upper range and a reduced prothrombin time of 45 per cent; these returned to preoperative levels by 1 month after surgery.

Pathological examination of the resected specimen confirmed the diagnosis of HCC (all grade pT_3) and severe cirrhosis in each patient. In addition the third patient had a marked superimposed acute alcoholic hepatitis.

After discharge from hospital, persistent tense ascites in patient 1 was treated by drainage of 6 litres of ascites at 1 and 2 months, and subsequently by insertion of a peritoneovenous shunt. Routine CT performed after 6 months was normal but after 1 year a bifocal recurrence in liver segments 7 and 8 was detected and treated by arterial chemoembolization. Liver transplantation was not considered because of persistent alcohol consumption. The patient currently remains well, without ascites, 30 months after surgery. The second patient was treated intensively for ascites that finally became responsive to medical management. He is currently well with no evidence of recurrence 23 months after surgery. The final patient died from liver failure with persistently high α-fetoprotein levels but without recurrence of symptoms 6 months after surgery. Autopsy was not

Table 1 Intraoperative and postoperative course in the three patients undergoing laparoscopic resection of hepatocellular carcinoma

	Patient 1	Patient 2	Patient 3
Duration of clamping (min)	45	40	37
Duration of surgery (min)	180	210	120
Intraoperative blood loss (ml)	200	100	400
Size of specimen (cm)	5 × 5 × 4	5 × 4 × 3	5 × 4 × 4
Postoperative ascites leak (days)	6	4	7
In-hospital stay (days)	10	6	9

performed. None of the patients had evidence of peritoneal or port-site metastases at the time of last evaluation.

Discussion

Laparoscopic liver resection has recently been shown by several groups to be safe, even in patients with a chronic underlying liver disease[11–16]. The alleged (although not yet proven) advantage is reduced postoperative pain and a shorter recovery time compared with that after open surgery[13]. An additional advantage of the laparoscopic approach, shown in the present study, is that resection can be performed in patients with decompensated liver cirrhosis that would have contraindicated conventional hepatectomy.

All three patients had a short life expectancy at the time of presentation. The median survival following treatment of small uncomplicated HCC in patients with Child's grade B and C disease is 16 and 2 months respectively[17]. Had HCC rupture occurred in any of the present patients their clinical condition would have further deteriorated, precluding any form of effective treatment.

At the time of surgery, all three patients were grade C according to Bismuth's modification of the Child's score[18] and had a risk score of more than 4 according to the classification of Nagashima *et al.*[19]. At this stage, the risk of postoperative liver failure and in-hospital death are in excess of 90 and 50 per cent respectively[18,19]. In contrast, the postoperative course of the patients in this study was relatively uneventful and all were discharged within 10 days of surgery.

Intractable ascites is one of the most frequent causes of in-hospital death after hepatectomy in patients with cirrhosis[20]. Its presence before operation is one of the most severe risk factors for fatal postoperative liver failure[19], even after a simple exploratory laparotomy[21]. Ascites is frequently associated with renal failure and, most importantly, with leakage through the abdominal wound preventing healing and encouraging infection. Although there was leakage through the port sites following laparoscopy, the incisions were much smaller and more anterior. In addition, no dissection of the falciform, triangular or round ligaments (where there is increased lymphatic flow in cirrhosis[22]) was required. Finally, the improved kinetics of the diaphragm following laparoscopic surgery, compared with open operation[23], may have helped the absorption of ascites.

Intraoperative blood loss has also been shown to be a major risk factor for postoperative death, in particular in patients with chronic underlying liver disease[24]. In the study of Takenaka *et al.*[24] mean perioperative blood loss following partial liver resection in patients with Child's grade A, B and C disease who died from liver failure after operation was 4, 5 and 6 litres respectively. In the present patients, blood loss was less than 500 ml, probably explained by clamping of the hepatic pedicle, the lack of extensive dissection and the counterpressure induced by the pneumoperitoneum.

Patients 2 and 3 underwent partial resection of the tumour with a 1-cm margin. Patient 1, however, had a tumour in segment 7, and could only undergo enucleation because the rigidity of the non-tumour-bearing liver precluded adequate bending of segments 4–6 to expose segments 7 and 8. Although his recurrence close to the resection margin was probably a consequence of insufficient resection, this patient simultaneously developed a recurrence in segment 8.

Laparoscopic access to tumours in liver segment 7 or 8 is difficult but probably not the only limit to laparoscopic partial liver resection. Haemodynamic instability due to massive bleeding of a ruptured HCC and tumour invasion of segmental, portal or suprahepatic veins are also contraindications to the laparoscopic approach.

A potential drawback of laparoscopic resection of HCC is the risk of tumour cell seeding in the peritoneal cavity, as described following laparoscopic resection of gallbladder and colorectal malignancies[25]. Experience suggests that this risk is not as high as previously thought, provided the tumour is not opened and is extracted in a specimen bag. Port-site metastases have not yet been reported following laparoscopic resection of HCC or liver metastasis. Furthermore, the development of skin metastases following percutaneous biopsy of HCC does not impair survival provided that such lesions are resected[26]. In patients with a ruptured HCC, tumour cells may already be present in the peritoneal cavity at the time of surgery. Peritoneal carcinomatosis, however, accounts for only 14 per cent of recurrences after ruptured HCC; two-thirds of peritoneal recurrences are associated with intrahepatic recurrence[27,28].

This study suggests that the laparoscopic approach to liver resection should not only be considered as an alternative to open surgery but also may enable resection in some patients considered unfit for open surgery.

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Original article

Early evaluation of renal reperfusion injury after prolonged cold storage using proton nuclear magnetic resonance spectroscopy

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Background: Proton nuclear magnetic resonance (NMR) spectroscopy can be used as a non-invasive tool to measure renal damage. In the present investigation, proton NMR spectroscopy of urine was assessed in order to detect cellular damage after different periods of cold ischaemia in two standard preservation solutions.

Methods: The isolated perfused pig kidney was used to assess initial renal function after *in situ* cold flush and cold storage (CS) for 24 or 48 h in two standard preservation solutions: EuroCollins (EC) and University of Wisconsin (UW) solutions. Kidneys flushed with cold heparinized saline and immediately perfused were used as a control group. Kidneys were perfused for 2 h at 37·5°C for functional evaluation. During reperfusion, renal perfusion flow rate was measured. Glomerular filtration rate (GFR), tubular reabsorption of sodium ions, and lactate dehydrogenase (LDH) and *N*-acetyl-β-D-glucosaminidase (NAG) excretion were determined. Impairment caused by ischaemia and reperfusion was also determined by histological techniques and proton NMR spectroscopy.

Results: The perfusion flow rate, GFR and tubular reabsorption of sodium were significantly decreased in experimental groups compared with the control group. There was no significant difference between experimental groups after 24 h of CS. The perfusion flow rate was significantly decreased in the EC group after 48 h of cold ischaemia compared with that in the UW group. After 48 h of CS, GFR and tubular reabsorption of sodium were significantly reduced in the EC group compared with those in the UW group. The release of LDH into the effluent and the urinary excretion of NAG were not significantly different after 24 h of CS. After more than 45 and 60 min of reperfusion respectively, LDH and NAG excretion was no different in the 48-h CS groups. The most relevant resonances determined by proton NMR spectroscopy were of citrate, trimethylamine-*N*-oxide, lactate, acetate and amino acids. Excretion of these markers was significantly more accurate and efficient to assess renal ischaemia–reperfusion injury than that of biochemical markers. A resonance (*P*) detected particularly in the EC group after 48 h of CS was identified and correlated well with renal dysfunction. After CS for 48 h and 2 h of reperfusion, renal injury was histologically more pronounced in EC groups than in UW groups. However, the difference was not significant after CS for 24 h.

Conclusion: NMR spectroscopy, which is a non-invasive and non-destructive technique, is more accurate and efficient when assessing kidney damage after cold ischaemia and reperfusion when compared to conventional histological and biochemical analysis.

Paper accepted 27 May 1999

British Journal of Surgery 1999, 86, 1401–1409

Introduction

In organ transplantation, reperfusion injury is difficult to assess because of the numerous factors that can lead to the same outcome: delayed organ function or non-function of the transplant. Consequently, postoperative care becomes more complex and appropriate administration of crucial but nephrotoxic immunosuppressive agents (e.g. cyclosporin) or diagnosis of rejection may be difficult in the presence of significant allograft dysfunction. The absence of immediate renal function after transplantation is usually known as delayed graft function and defined as the need for one or more than one dialysis session during the postoperative period, which in some instances may aggravate ischaemic renal injury, prolonging the renal impairment. In fact, this clinical definition probably detects only the most severe cases of impaired renal function caused by ischaemia–reperfusion injury. Acute tubular necrosis is the pathological diagnosis and one of the major causes of early dysfunction of transplanted kidneys[1].

Ischaemic renal injury, including injury to transplants, results in functional impairment and structural damage followed by a stereotypic inflammatory response consisting of an influx of T cells and macrophages. Currently, the assessment of graft function following transplantation is determined by the measurement of plasma creatinine or blood urea nitrogen. Many compounds have been measured in urine, and attempts have been made to correlate their levels with diagnosis and prognosis of acute renal failure. Determination of urinary excretion of specific enzymes and proteins as possible markers of renal allograft dysfunction has been studied extensively[2]. However, none of these markers, either for native or allograft kidneys, has been rigorously demonstrated to be reliable in the diagnosis of acute renal failure. The detection of early dysfunction results in more frequent use of invasive testing methods such as renal biopsy which often gives inconclusive histological results and the monitoring of immunosuppressive therapy where possible. Consequently, the differential diagnosis of graft dysfunction is often based on an individual patient's response to therapy.

In recent years, proton nuclear magnetic resonance (NMR) spectroscopy has been established as a powerful non-destructive and non-invasive technique that can provide complete structural analysis of a wide range of organic molecules in biological fluids in various pathological conditions. Recently, this technology has been applied to the study of biological fluids such as plasma, urine, bile, and seminal or synovial fluids[3,4].

The present study was undertaken to test the hypothesis that proton NMR spectroscopy is an efficient technique compared with evaluation of conventional biochemical markers for detection of tubular damage after different cold preservation periods in two commonly employed standard preservation solutions (EuroCollins (EC) and University of Wisconsin (UW)) and normothermic reperfusion. For this purpose the isolated perfused kidney model was used to assess precisely initial renal function at the time of reperfusion. The isolated perfused kidney allows direct experimental manipulation of fully differentiated mature tubule cells. The pig kidney was chosen because there is no accurate information about cold ischaemia and reperfusion injury in this model.

Materials and methods

This study was approved by the institutional review committee. The animals were cared for in accordance with university and national guidelines. Large white male pigs weighing 30–35 kg (INRA, Le Magneraud, Surgères, France) were used.

Preservation

UW and EC solutions were used to flush and to preserve kidneys in this study. Kidneys were cold flushed *in situ* with the preservation solution and preserved at 4°C for 24 or 48 h, after which the organs were studied on the isolated perfused circuit. Warm ischaemia was negligible before reperfusion.

Reperfusion in the isolated perfused kidney model

Kidneys were harvested as described previously[5,6] and were randomized into five groups (*Table 1*): group 1

Table 1 Experimental design

	Group 1 (*n*=6)	Group 2 (*n*=8)	Group 3 (*n*=8)	Group 4 (*n*=8)	Group 5 (*n*=8)
Cold storage (h)					
EC solution	–	24	–	48	–
UW solution	–	–	24	–	48
Urine production (ml/h)*					
0–60 min of reperfusion	126(3)	49(2)	50(2)	22(1)	38(1)
60–120 min of reperfusion	132(3)	48(2)	47(2)	23(1)	35(1)

*Values are mean(s.e.m.). After preservation, kidneys were reperfused immediately for the functional study. EC, EuroCollins; UW, University of Wisconsin (control group, $n=6$), perfused immediately after cold flush with heparinized saline; group 2 ($n=8$), cold flush followed by cold storage (CS) for 24 h in EC solution; group 3 ($n=8$), cold flush followed by 24 h of CS in UW solution; group 4 ($n=8$), cold flush followed by CS for 48 h in EC solution; and group 5 ($n=8$), cold flush followed by 48 h of CS in UW solution. Control kidneys were attached to the isolated perfused circuit immediately after harvesting, and the experimental kidneys after cold storage. The organs were perfused for 2 h via the renal artery. The reperfusion medium was a freshly prepared Krebs solution containing the following electrolytes: sodium chloride 120 mmol/l, sodium bicarbonate 25 mmol/l, potassium chloride 4·8 mmol/l, magnesium sulphate 1·2 mmol/l, calcium chloride 1·2 mmol/l, monopotassium phosphate 1·2 mmol/l and D-glucose 11 mmol/l. The solution also contained dialysed bovine serum albumin (fraction V; Sigma, St Louis, Missouri, USA) 5·0 g per 100 ml, creatinine (Sigma) 10 mg/l and 5 ml of a 22-L-amino-acid mixture from a commercial solution (Clintec Nutrition Clinique, Sèvres, France). The solution was perfused in a closed thermostatically controlled circuit at 37·5°C. The perfusion flow rate was adjusted to maintain renal arterial perfusion pressure at 100 mmHg. Perfusion was provided by a peristaltic pump (BSM 1; Hospal, Lyon, France). Perfusion pressure was measured by a pressure transducer (Statham P23 Dc; Grass, Quincy, Massachusetts, USA). The outflow from the pump passed through a hollow-fibre type oxygenator (0600 ECM; Sciences Medical, Minneapolis, Minnesota, USA) in which the perfusate was oxygenated with a gas mixture (95 per cent oxygen and 5 per cent carbon dioxide) to maintain the pH at 7·40–7·45. An in-line filter (5-µm pore size) was used during perfusion to remove small debris from the circulation. Perfusion flow rate and perfusion pressure were monitored continuously. After a total of 15 min of equilibration, when a steady state had been achieved, perfusion flow rate (millilitres per minute per gram of tissue), glomerular filtration rate (GFR) (microlitres per min per g of tissue), tubular reabsorption of sodium ions (per cent), release of the cytosolic enzyme lactate dehydrogenase (LDH) (determined by an automat Ektachem (Kodak, Paris, France) apparatus) in effluent and *N*-acetyl-β-D-glucosaminidase (NAG) excretion in urine (Boehringer, Paris, France) were monitored at 15, 30, 45, 60, 75 and 90 min after the start of reperfusion. GFR was calculated from creatinine clearance using the formula GFR = urine flow rate × urine creatinine/perfusate creatinine. Tubular reabsorption of sodium ions was calculated as 100 × (1 − urine sodium ion concentration/perfusate sodium ion concentration × perfusate creatinine/urine creatinine). Sodium level was measured by flame photometry and creatinine was determined enzymatically.

Nuclear magnetic resonance spectroscopy

Urine and perfusate samples from isolated perfused kidneys were collected after each period of reperfusion and frozen at −20°C; NMR measurements were performed within 1 week. Perfusate was collected on sodium fluoride–oxalate. Samples were thawed at room temperature and prepared with 10 per cent deuterium oxide containing 0·75 per cent sodium 3-(trimethyl-2,2,3,3)-1-propionate) to reference the chemical shifts (0 parts per million) in 5-mm NMR tubes. Spectra were acquired at 400 MHz on a Bruker AM400WB (Bruker, Milton, Ontario, Canada) apparatus. The water signal was suppressed with low-power irradiation (0·8 W for 2 s). Spectra were acquired with 16000 data points for a spectral width of 6024 Hz with a 5-ms pulse (60°) and 128 scans were accumulated. The Fourier transform was performed on 16000 data points without filtering. Resonances were identified from published chemical shift data or by addition of standard compounds when necessary. As line widths of the peaks were equivalent, intensities of resonance were assessed by measuring peak heights taking into account the spin–spin coupling pattern, and were compared with the intensity of creatinine resonance. For urine NMR spectra, the ratios of citrate, trimethylamine-*N*-oxide, lactate, acetate and amino acids to creatinine were calculated and expressed in mmoles per mole of creatinine to take into account the influence of different urinary flow rates. In the case of an unidentified resonance, the intensity of resonance was assessed by measuring peak height and expressed in mmoles of hydrogen ions per mole of creatinine.

Histopathological analysis

At the end of the cold flush, after 24 and 48 h of CS and reperfusion, kidney samples were collected for light and electron microscopy. Samples were fixed with Dubosq–Brasil and 10 per cent formalin in phosphate buffer 0·01 mmol/l (pH 7·42) and embedded in paraffin. Conventional stains were applied (haematoxylin and eosin, periodic acid–Schiff). Analysis of the cellular ultrastructure using electron microscopy was also performed. Small pieces of renal tissue were fixed in 2·5 per cent glutaraldehyde, washed and postfixed in 2 per cent osmium tetroxide for 2 h at 4°C. After dehydration with ethanol, they were embedded in Araldite (Fluku, Buchs, Switzerland). Ultrathin sections were stained with uranyl acetate and lead citrate, and then examined under an electron microscope (100 CX; JEOL, Tokyo, Japan). Histological analysis concerned proximal tubular cells and particularly the brush border. Light and electron microscopic studies were reviewed by a pathologist blinded to the treatment groups.

Light microscopic sections were examined for cell vacuolization, tubular necrosis, tubular dilatation, intratubular detachment and interstitial oedema. At electron microscopy, brush border, intracellular oedema and organelles such as mitochondria were studied. Histological lesions were expressed according to the percentage of kidney samples affected using a semiquantitative scale: 1, no abnormality; 2, mild lesions affecting 10 per cent of kidney samples; 3, lesions affecting 25 per cent of samples; 4, lesions affecting 50 per cent of samples; and 5, lesions affecting more than 75 per cent of samples.

Statistical analysis

Results were expressed as mean(s.e.m.) and compared using variance analysis and the Student–Newman Keuls test for multiple comparisons. When a non-parametric test was needed, the Kruskal–Wallis analysis was used. The frequency of occurrence of *P* resonance was analysed on a contingency table with a χ^2 test. $P < 0{\cdot}05$ was considered statistically significant. Control group values are shown in figures and tables as reference values but were not used for statistical analysis.

Results

Functional results and injury markers

Fig. 1 summarizes the effects of cold ischaemia on renal function in the isolated perfused kidney model. Experimental groups, urine output and preservation conditions are summarized in *Table 1*. The perfusion flow rate was significantly reduced after cold preservation particularly after CS for 48 h in EC compared with UW solution. The GFR was also significantly reduced compared with that in controls. After CS for 24 h, the GFR was not significantly different for reperfusion times of less than 75 min. After 48 h of CS, the GFR was significantly higher in group 5 than in group 4. Tubular reabsorption of sodium was significantly decreased in cold-stored groups (groups 2–5) compared with that in group 1. After 24 h of CS, tubular reabsorption of sodium was not significantly different between groups 2 and 3 during reperfusion. After 48 h, tubular reabsorption of sodium was improved after preservation in UW solution in this model. After CS for 24 h, LDH release and NAG excretion were not significantly different. Between 15 and 45 min of reperfusion after CS for 48 h, kidneys in group 4 showed a greater release of LDH in urine than did those in group 5. The difference was not statistically significant after 45 min. NAG excretion was not significantly different in groups 4 and 5 by 60 min after the start of reperfusion.

Nuclear magnetic resonance spectroscopy results (*Fig. 2*)

In urine NMR spectra, the lactate to creatinine ratio during reperfusion was significantly greater in urine from kidneys preserved with EC solution than in those preserved with UW solution or controls. The acetate to creatinine ratio was significantly increased in urine from kidneys perfused with EC (groups 2 and 4) compared with that in UW groups (groups 3 and 5) particularly after CS for 48 h. The trimethylamine-*N*-oxide to creatinine ratio was significantly higher in urine from groups 2 and 4 than from groups 3 and 5. Trimethylamine-*N*-oxide was not detected in urine from the control group. Amino acid reabsorption was significantly decreased in urine from kidneys preserved with EC compared with UW solution. Citrate excretion was detected mainly in urine from controls and groups 3 and 5. *P* was detected on urine spectra in the chemical shift range δ 1·4–1·5 from preserved kidneys particularly in EC groups (*Fig. 2*). This resonance was detected in urine from four of eight kidneys in group 2 *versus* one of eight in group 3 ($P < 0{\cdot}001$), and all eight in group 4 *versus* four of eight in group 5 ($P < 0{\cdot}01$).

Histological analysis

Under light microscopy, sections obtained from control kidneys displayed normal renal architecture after cold flush and very minimal change after reperfusion. At the end of normothermic reperfusion, control kidneys exhibited only very localized oedema. After CS for 24 h and 2 h of reperfusion, there was no significant difference between groups 2 and 3. However, after CS for 48 h and reperfusion, damage was apparent particularly in group 4 (*Table 2*). After reperfusion, kidneys flushed and preserved with EC solution (group 4) showed significantly higher mean scores than those flushed and preserved with UW solution (group 5) (*Table 2*). These differences were more pronounced with respect to tubular dilatation, intratubular cell detachment and cast formation, tubular cell brush border integrity and interstitial oedema. At electron microscopy, kidneys from the control group were unchanged after reperfusion, and had a well preserved brush border. After CS and reperfusion, kidneys preserved with EC solution had more pronounced histological alterations at 48 h than those preserved with UW solution (*Table 2*). Mitochondrial depletion and disintegration were significantly greater in kidneys from EC groups than in those from UW groups, particularly after 48 h.

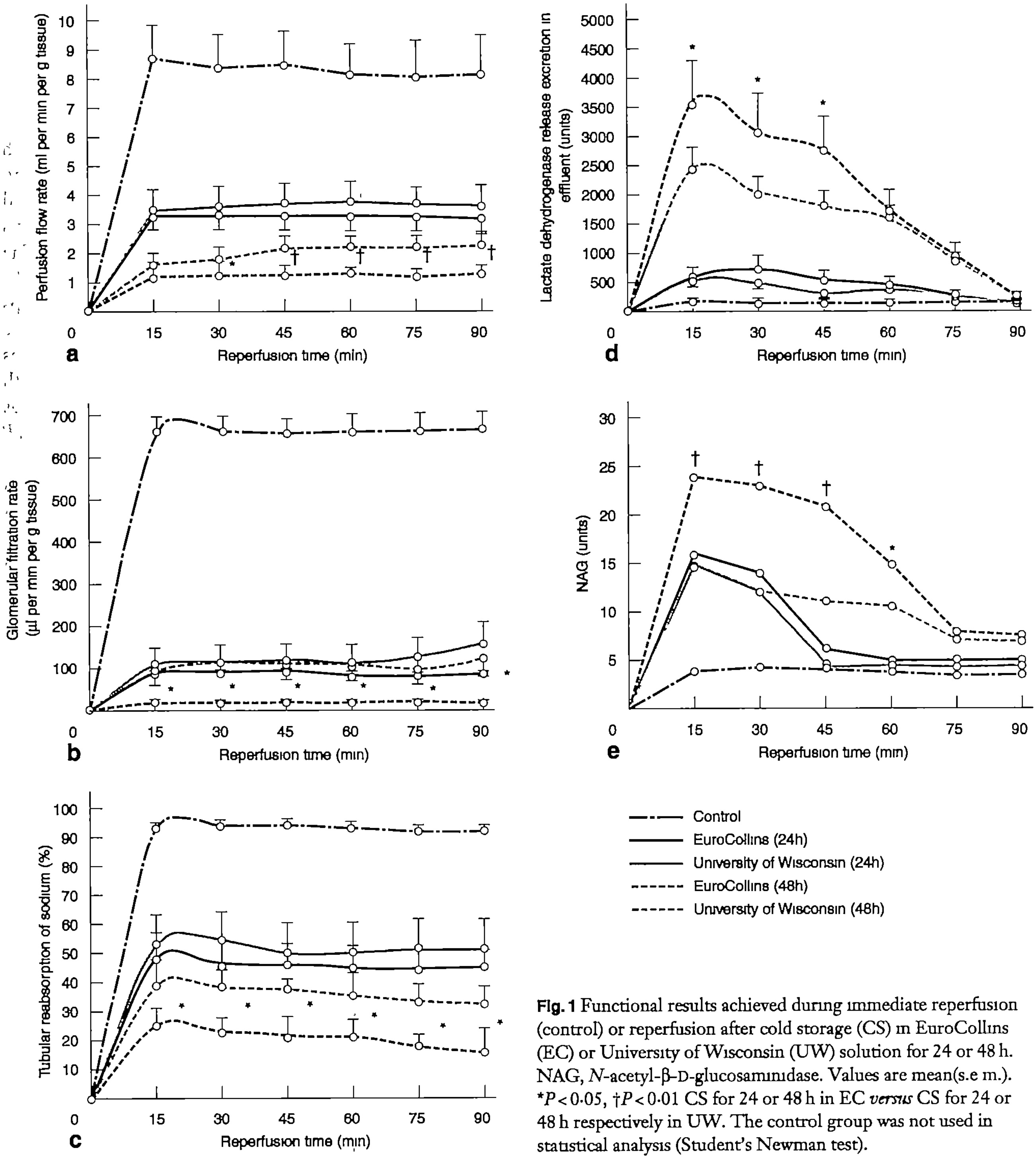

Fig. 1 Functional results achieved during immediate reperfusion (control) or reperfusion after cold storage (CS) in EuroCollins (EC) or University of Wisconsin (UW) solution for 24 or 48 h. NAG, *N*-acetyl-β-D-glucosaminidase. Values are mean(s.e.m.). $^*P < 0.05$, $^\dagger P < 0.01$ CS for 24 or 48 h in EC *versus* CS for 24 or 48 h respectively in UW. The control group was not used in statistical analysis (Student's Newman test).

Discussion

It has become increasingly evident that the clinical expression of ischaemia–reperfusion, delayed graft function, influences the development of acute rejection and late graft dysfunction[7,8]. Reperfusion injury is the result of a cascade of events, making the allograft an inflamed organ which may stress the parenchyma and vessels, and promote fibrosis. Injury may increase expression of major histocompatibility antigens in epithelium and endothe-

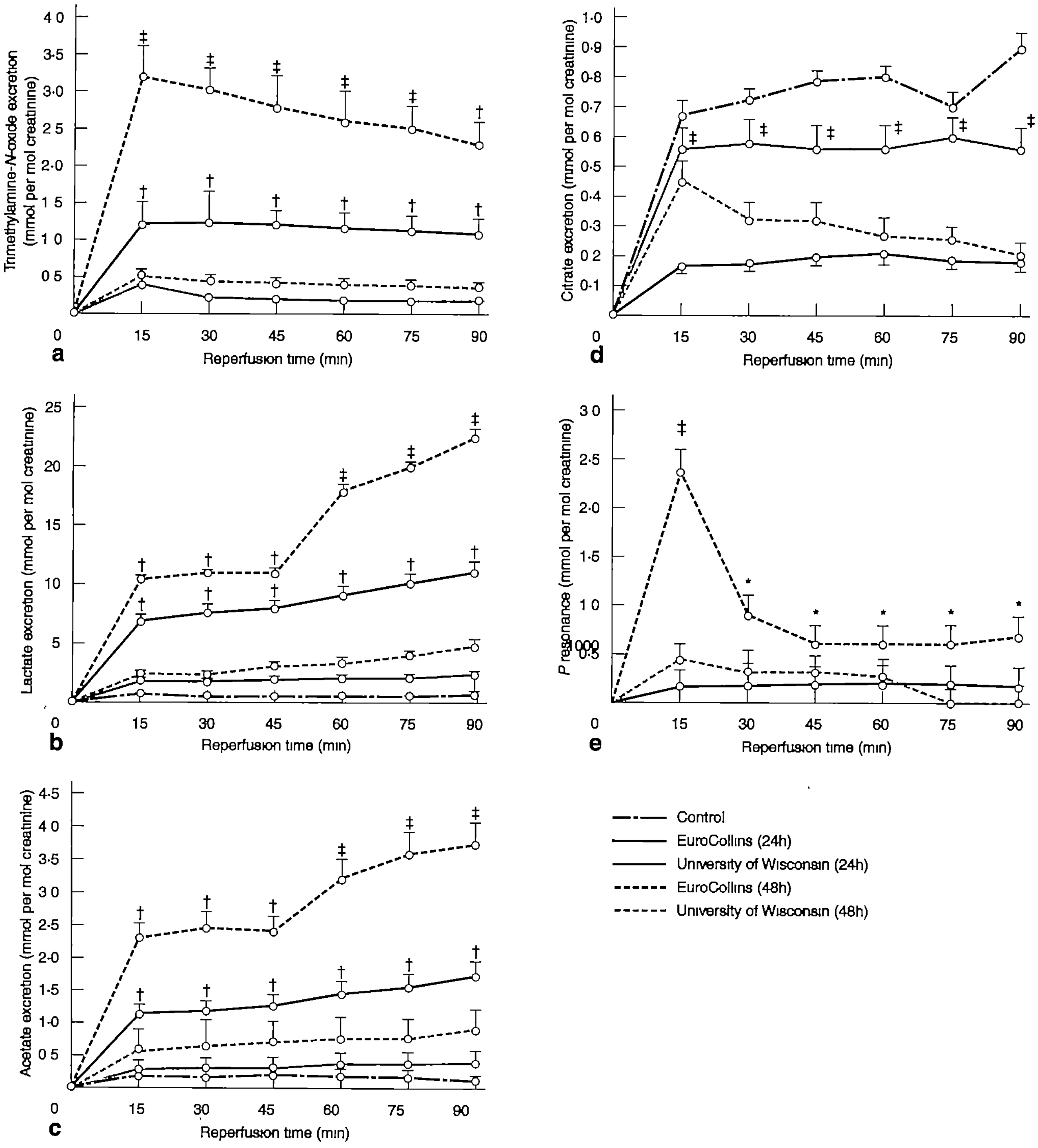

Fig. 2 Proton nuclear magnetic resonance spectroscopy markers during immediate reperfusion (control) or reperfusion after cold storage (CS) in EuroCollins (EC) or University of Wisconsin (UW) solution for 24 or 48 h. Values are mean(s.e.m.). Trimethylamine-*N*-oxide was not detected in the control group and was increased after CS for 24 and 48 h in EC solution. Lactate and acetate excretion was increased in the EC groups. Citrate was detected in control, EC (24 h), UW (24 h) and UW (48 h) groups. *P* resonance was not detected in control and UW (24 h) groups. $^*P < 0.05$, $^\dagger P < 0.01$, $^\ddagger P < 0.001$ CS for 24 or 48 h in EC *versus* CS for 24 or 48 h respectively in UW. The control group was not used in statistical analysis (Student's Newman test)

Table 2 Histopathological evaluation of kidneys after 2 h of normothermic perfusion

		24 h		48 h	
	Control	EC	UW	EC	UW
Vacuolization	1	3	2·5	4	3
Tubular necrosis	1	2·5	2	5	3
Tubular dilatation	1	3	3	4	4
Cell detachment	1	3	3	5	4
Brush border	1·5	3	2·5	4	3
Intracellular oedema	1	3	3	5	4
Interstitial oedema	1	3	2·5	4	4
Mitochondrial disintegration	1	3	2·5	4	2
Tubular membrane integrity	1·5	2	2	4	3
Score*	1·1(0·1)	2·8(0·1)	2·5(0·1)	4·3(0·1)	3·3(0·2)†

*Values are mean(s.e.m.). EC, EuroCollins; UW, University of Wisconsin. †$P < 0.05$ UW *versus* EC (48 h) (Student's Neuman test)

lium as well as recruiting and activating antigen-presenting cells[7].The rate of delayed graft function in cadaveric renal transplantation is between 10 and 60 per cent, and makes the diagnosis of rejection more difficult, prolongs hospital stay and may increase the incidence of acute rejection and favour chronic transplant nephropathy[9]. This results in more frequent use of invasive testing methods such as renal allograft biopsy, which is the gold standard for obtaining accurate diagnostic information about allograft dysfunction due to cellular rejection, recurrent disease or drug-induced toxicity. A recent report demonstrated that a correct histopathological diagnosis was correlated with the clinical and biological diagnosis only 43 per cent of the time[10]. However, clinically relevant complications are observed in 3·5–21 per cent following percutaneous biopsy and pose a risk for the transplant patient[11,12]. In addition, the use of potentially nephrotoxic immunosuppressive compounds may enhance ongoing tubular injury when full doses are continued or expose the recipient to an increased risk of rejection when the dosage is reduced. Consequently, new strategies must be directed towards the development of non-invasive methods of detecting allograft inflammation.

The main object of this study was to determine whether proton NMR spectroscopy was able to detect renal damage when compared with excretion of enzymes into the urine or histological analysis. The abnormal excretion of trimethylamine-*N*-oxide determined by NMR spectroscopy was noted particularly in EC groups and after 48 h of cold ischaemia. Trimethylamine-*N*-oxide is derived from renal medullary organic osmolytes to counteract perturbation of proteins by a high urea concentration and to fill the osmotic gap between intracellular and extracellular fluids. This osmolyte has been identified exclusively in the intracellular compartment of the renal inner medulla[13]. A raised urinary level of this compound is related to leakage from damaged medullary cells in different models of renal damage[5]. This marker is well correlated with the reduction in perfusion flow rate which reflects the constrictive response of the renal vascular bed to the ischaemic insult. After a combination of normothermic ischaemia and cold preservation in EC solution using an identical model, the authors demonstrated previously that trimethylamine-*N*-oxide excretion in urine was related to more intense medullary damage[5]. Trimethylamine-*N*-oxide has also been detected in clinical situations following acute toxic exposure to drugs or other xenobiotics (ifosfamide or phenol)[14,15] or in chronic disease, where increased excretion of trimethylamine-*N*-oxide was related to damage to tubule cells and medullary damage[16]. Because the vast majority of early renal dysfunction after reperfusion is due to acute tubular necrosis in the outer renal medulla, trimethylamine-*N*-oxide could be a relevant marker of graft damage.

The other relevant resonances used to evaluate renal function after transplantation were those arising from lactate, citrate and acetate. Lactate excretion was also significant in EC groups. This acid is normally reabsorbed in the proximal tubule and abnormal excretion is due to dysfunction of the proximal tubule and/or an increase in lactate production by renal cells related to the anaerobic conditions during cold ischaemia. The increased lactate excretion in EC groups is related to proximal tubular injury. Citrate is an organic acid normally found in urine; it is produced from the reaction between acetyl-coenzyme A and oxaloacetate, which represents the first step of the Krebs cycle. In the proximal tubule, citrate is reabsorbed by an apical sodium–citrate co-transporter and then is metabolized by two potential pathways, either cytoplasmic metabolism via adenosine 5′-triphosphate citrate lyase or mitochondrial metabolism. Reduced citrate excretion is indicative of impaired oxidative damage[3,17–20]. These results demonstrate an impairment of Krebs cycle function and a proximal tubular dysfunction correlated with amino aciduria after cold preservation with EC solution compared with UW solution. In the present model, trimethylamine-*N*-oxide, lactate, acetate and citrate excretion associated with the detection of resonance *P* in urine could accurately discriminate kidneys with significant renal medullary damage when compared to other conventional parameters and histological analysis. No other method is able to determine, in the same experiment, the presence of amino acids, glucose or lactic acid and consequently to map renal injuries to different tubular segments. By collecting serial urine samples, the natural history of the injury can be followed by NMR spectroscopy.

Although during reperfusion all LDH in the effluent originates from the kidney, it remains unclear which renal cells are damaged. Also, LDH is present in almost all living cells and is probably released into the perfusate by damaged erythrocytes which are trapped in the renal microvasculature. This lack of specificity may explain why in this study LDH could not distinguish between experimental groups, particularly after 24 h of preservation. NAG, which is a lysosomal enzyme abundant in proximal tubular segments, has been a useful marker of tubular damage. However, in this model, excretion of NAG was not very effective in quantifying tubular damage between experimental groups particularly after 24 h of CS and after 60 min of reperfusion in 48 h preserved group. In addition, the wash out of NAG may explain why in this study NAG could not distinguish damaged grafts.

Proton NMR spectroscopy of urine has been used previously to investigate renal allograft dysfunction[19,20]. However, the influence of preservation solution was not studied and it was not specified if kidneys were retrieved from multiple organ or single organ donors. In addition, in these reports, patients receiving a kidney from living related donors were studied with patients transplanted with a cadaver kidney. This experimental condition implied that cold ischaemia was very different[19]. However, a resonance at 3·7 p.p.m. (*P*3·7) in the 24-h urine from patients who underwent renal transplantation was detected and the intensity of this resonance could be better than conventional biochemical measures as an indicator of the amount of cyclosporin during this period. The respective variations in this metabolite in urine could contribute to prognosis and diagnosis of renal function impairment related to cyclosporin toxicity or overdose, or to rejection[19,20].

The present research could stimulate further development of preservation methods to reduce cold ischaemia–reperfusion injury. Early ischaemia and reperfusion, if severe enough in a single kidney, may be an important antigen-independent risk factor for later renal deterioration and failure[21]. The vast majority of the markers detected by proton NMR spectroscopy are intracellular. Consequently, these markers could be assessed directly within the kidneys during CS in their sterile containers. This non-invasive evaluation could be combined with other NMR techniques such as phosphate-31 NMR spectroscopy to measure the relative intracellular concentrations of several phosphorus metabolites or the evaluation of intracellular and extracellular pH during CS. An overall reduction of non-function to below 20 per cent is probably not feasible with the CS preservation method and machine perfusion could be considered as a relatively simple alternative to improve the outcome after kidney transplantation[22]. Because only preparation of the sample is needed and a small volume is required, NMR spectroscopy may also be a valuable aid for the evaluation of the effect of haemodynamic instability or hypoperfusion from donors, particularly in intensive care units.

In conclusion, non-invasive and non-destructive spectroscopic assessment of ischaemia–reperfusion injury and renal medullary injury by proton NMR spectroscopy represents a novel approach to the monitoring of renal transplant function and may improve the management of patients during the early period after renal transplantation.

Acknowledgements

This work was supported in part by grants from the Association pour le Développement de la Dialyse à Domicile en Charente Marentime (ADA 17), the Conseil Régional Poitou Charente and Faculté de Médecine de Poitiers.

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Original article

Kupffer cell blockade, tumour necrosis factor secretion and survival following endotoxin challenge in experimental biliary obstruction

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Background: Gram-negative sepsis and its sequelae frequently complicate invasive procedures in patients with obstructive jaundice. In response to endotoxin, Kupffer cells secrete tumour necrosis factor (TNF), a pivotal early mediator of sepsis. An investigation was carried out into the specific role of Kupffer cell TNF secretion following endotoxin challenge in obstructive jaundice.
Methods: Survival following intraperitoneal administration of endotoxin (2·0, 0·02 and 0·0002 mg per 100 g) was determined in rats following bile duct ligation (BDL) or sham operation. Plasma TNF concentration was quantified following endotoxin administration (0·0002 mg per 100 g) at 1, 2 and 6 h. Subsequently, the effect of Kupffer cell blockade by gadolinium chloride on survival and plasma TNF concentration was assessed.
Results: Jaundiced animals showed a significantly increased mortality rate following intraperitoneal injection of endotoxin 2·0 mg per 100 g (BDL 100 per cent *versus* sham 0 per cent) and 0·02 mg per 100 g (BDL 70 per cent *versus* sham 0 per cent; $P = 0.002$, Fisher's exact test). Median plasma TNF concentration was significantly greater in jaundiced animals 1 h after endotoxin administration (BDL 943 (interquartile range (i.q.r.) 211–3900) pg/ml *versus* sham 64 (i.q.r. 47–127) pg/ml; $P = 0.002$, Mann–Whitney *U* test). Kupffer cell blockade with gadolinium chloride increased the survival rate following endotoxin administration in BDL animals (BDL-$GdCl_3$ 100 per cent *versus* BDL-saline 40 per cent; $P = 0.0003$, Fisher's exact test) and decreased median plasma levels of TNF (BDL-$GdCl_3$ 88 (i.q.r. 0–1065) pg/ml *versus* BDL-saline 16 550 (1255–29 360) pg/ml; $P = 0.002$, Mann–Whitney *U* test).
Conclusion: Kupffer cell blockade improved survival and suppressed systemic TNF activity after endotoxin challenge. In obstructive jaundice, hypersecretion of TNF by Kupffer cells may supplement systemic cytokine production and be responsible for significant complications.

Presented to the Surgical Research Society, Oxford, UK, January 1996, and published in abstract form as *Br J Surg* 1996; **83**: 705–6
Paper accepted 28 June 1999

British Journal of Surgery 1999, **86**, 1410–1414

Introduction

Invasive procedures are frequently followed by septic and sepsis-related complications in patients with obstructive jaundice[1–3]. Intestinal derived endotoxaemia is implicated in the pathophysiology of these events. Previous studies have suggested impaired endocytic function of the mononuclear phagocytic system as a mechanism of endotoxaemia in biliary obstruction[4]. An additional function of the mononuclear phagocytic system is the secretion of pro-inflammatory cytokines. *In vitro* studies of Kupffer cell function have demonstrated hypersecretion of tumour necrosis factor (TNF) and interleukin (IL) 6 in obstructive jaundice[5]. Although these data have been derived from studies on the physiologically intact liver using an *in situ* hepatic perfusion system, the significance of these findings has not been established *in vivo*.

The aim of these experiments was to elucidate the role of the Kupffer cell population in the response to endotoxin challenge in experimental obstructive jaundice *in vivo*.

Materials and methods

A total of 180 immunologically mature male Wistar rats (weight 275–325 g) were used in this study. Control animals underwent sham operation. Following the administration of anaesthesia using intramuscular injection of ketamine 6 mg per 100 g (Parke-Davis Veterinary, Gwent, UK) and xylazine 0·7 mg per 100 g (Bayer, Bury St Edmund's, UK), laparotomy was performed through a 1·5-cm upper midline incision. In animals undergoing bile duct ligation (BDL), 1 cm of the bile duct was mobilized, doubly ligated and divided. Sham operation entailed laparotomy and mobilization of the bile duct only. Animals had access to water and standard chow *ad libitum* throughout the experimental period. All experiments were conducted in compliance with UK Animals (Scientific Procedures) Act 1986.

Experiment 1: characterization of *in vivo* response to endotoxin in experimental obstructive jaundice

Some 3 weeks after BDL or sham procedure, animals were assigned to one of three groups comprising ten jaundiced and ten sham animals. The three groups were challenged with differing doses of intraperitoneal endotoxin B40111 (Sigma Aldrich, Poole, UK): 0·0002, 0·02 and 2·0 mg per 100 g. Survival was assessed at 4 h; animals were anaesthetized and blood was sampled by direct cardiac puncture. Samples were immediately placed on ice, centrifuged at 2000 r.p.m. for 10 min at 4°C and stored at – 70°C pending assay.

To quantify the dynamics of TNF secretion following septic challenge a further group of animals was studied. Some 3 weeks after BDL or sham operation, animals were assigned to one of three groups comprising ten BDL and ten sham-operated animals. All animals were challenged with a sublethal dose of intraperitoneal endotoxin (0·0002 mg per 100 g). Animals in group 1 were killed at 1 h, those in group 2 at 2 h, and group 3 at 6 h. Animals were anaesthetized and blood was sampled by cardiac puncture. Samples were collected and plasma was stored as outlined above for TNF analysis.

Experiment 2: effect of Kupffer cell blockade with gadolinium chloride on survival and systemic tumour necrosis factor secretion

On day 19 following BDL, 60 jaundiced animals were randomized to receive intraperitoneal gadolinium chloride (Sigma Aldrich) 10 mg per 100 g or saline. On day 21, 20 animals from each group were challenged with intraperitoneal endotoxin (0·02 mg per 100 g) and survival was assessed 4 h later. The remaining ten animals in each group were then challenged with a sublethal dose of endotoxin (0·0002 mg per 100 g) and killed at 1 h. Blood was sampled by cardiac puncture following induction of anaesthesia and plasma was stored as outlined above for TNF analysis.

TNF assay

Immunoreactive TNF in plasma and perfusate was measured using an enzyme-linked immunosorbent assay technique developed in the authors' laboratory[6]. Briefly, a 96-well microtitre plate was coated with monoclonal antibody to murine TNF (TN3 19.12, donated by Celltech, Slough, UK) which exhibits a high degree of cross-reactivity to rat TNF. TNF bound to the solid phase was detected using rabbit polyclonal antimurine TNF antibody (Bradsure Biologicals, Loughborough, UK) and donkey antirabbit horseradish peroxidase conjugate (Jackson Immunoresearch, West Grove, Pennsylvania, USA). Absorbance was read at 490 nm. The detection limit of the assay was 39·0 pg/ml, the interassay coefficient of variation was 10 per cent and the intra-assay coefficient of variation 11 per cent.

Histological confirmation of Kupffer cell depletion by gadolinium chloride

Sections of liver from jaundiced animals given gadolinium chloride ($n = 4$) or saline ($n = 4$) were perfused fixed with 4 per cent paraformaldehyde before processing through ascending alcohols and toluene to paraffin wax. The monoclonal mouse antibody ED1 (Serotec, Oxford, UK) recognizes a single-chain glycoprotein expressed by resident and recruited rat hepatic macrophages, and was used as a Kupffer cell marker[7]. Thin sections (3 µm) were cut and adhered to slides coated with 3-aminopropyltriethoxysaline (Sigma Aldrich) for 24 h at 37°C, dewaxed and rehydrated. Endogenous peroxidase was blocked for 5 min by incubation with 3 per cent hydrogen peroxide in alcohol. Slides were incubated with 4 per cent normal rabbit serum in phosphate-buffered saline (PBS) for 30 min at room temperature before incubation with a 1 : 200 dilution of ED1 in PBS for 1 h at room temperature. After washing, a 1 : 200 dilution of biotinylated fragment in PBS of affinity-purified rabbit antimouse immunoglobulin F(ab′)$_2$ (Dako, Glostrup, Denmark) preincubated with 4 per cent normal rat serum was applied to slides for 30 min at 37°C. Slides were washed with PBS before incubation with strepavidin–biotin–horseradish peroxidase complex (Dako) for 30 min. A final PBS wash was followed by the application of 3,3′-diaminobenzidine tetrahydrochloride (Sigma Aldrich) activated with 50 ml of 3 per cent hydrogen peroxide diluted 1 : 20 in distilled water for 5 min. Slides were counterstained with haematoxylin. ED1-positive hepatic macrophages were counted in ten high-powered fields (h.p.f.) on each liver section by an independent investigator unaware of the specimen group, and a mean for each liver section was determined.

Statistical analysis

Statistical analysis was carried out with the Mann–Whitney *U* test. Fourfold table analysis was by Fisher's exact test. Significance was taken at the 5 per cent level. Results are expressed as median (interquartile range (i.q.r.)). Analysis was performed using the software package Arcus Pro-Stat (Iain E. Buckan, Oxford, UK).

Results

Survival following intraperitoneal endotoxin

Following BDL, animals were highly sensitive to a dose of endotoxin (2·0 mg per 100 g) readily tolerated by sham-operated animals for up to 4 h. At 1–2 h after intraperitoneal endotoxin injection, BDL animals showed diminished spontaneous movement around the cages and developed tachycardia, tachypnoea and piloerection. All BDL animals had died at 4 h. Sham animals behaved normally throughout. Reducing the dose of endotoxin to 0·02 mg per 100 g resulted in a 30 per cent survival rate in jaundiced animals at 4 h ($P = 0{\cdot}21$ *versus* BDL animals given endotoxin 2·0 mg per 100 g, $P = 0{\cdot}002$ *versus* sham animals given 0·02 mg per 100 g, Fisher's exact test). Further reduction of the dose of endotoxin to 0·0002 mg per 100 g produced a consistent 100 per cent survival rate at 4 h in BDL animals ($P = 0{\cdot}005$ *versus* BDL animals given endotoxin 2·0 mg per 100 g, Fisher's exact test).

Systemic tumour necrosis factor response following intraperitoneal endotoxin

The plasma TNF profile in BDL and sham animals measured after the intraperitoneal injection of a sublethal dose of endotoxin (0·0002 mg per 100 g) demonstrated maximal secretion by both jaundiced and sham animals at 1 h. The magnitude of this response was significantly greater in BDL animals (*Fig. 1*). There was no significant difference in plasma TNF levels between jaundiced and sham animals at 2 h ($P = 0{\cdot}79$) and 6 h ($P = 0{\cdot}33$).

Effect of Kupffer cell blockade

Survival

Kupffer cell blockade by gadolinium chloride attenuated the lethal effects of endotoxin (0·02 mg per 100 g) at 4 h compared with survival in saline-treated jaundiced animals (*Fig. 2*).

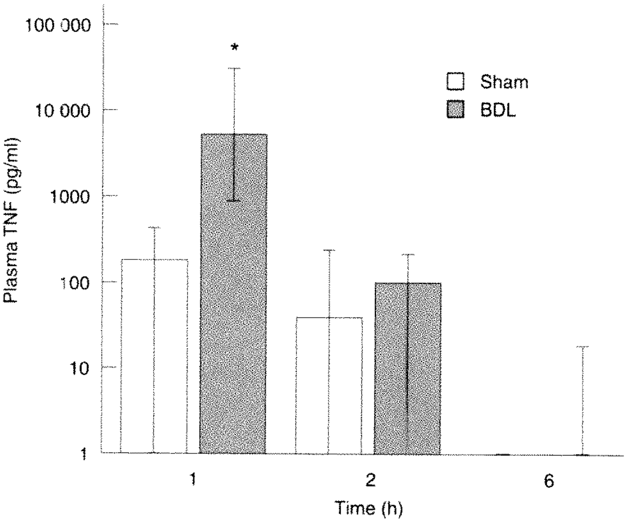

Fig. 1 Plasma tumour necrosis factor (TNF) concentration following intraperitoneal administration of endotoxin 0·0002 mg per 100 g. *$P = 0{\cdot}002$ *versus* sham operation at 1 h; $P = 0{\cdot}0005$ *versus* bile duct ligation (BDL) at 2 h (Mann–Whitney *U* test)

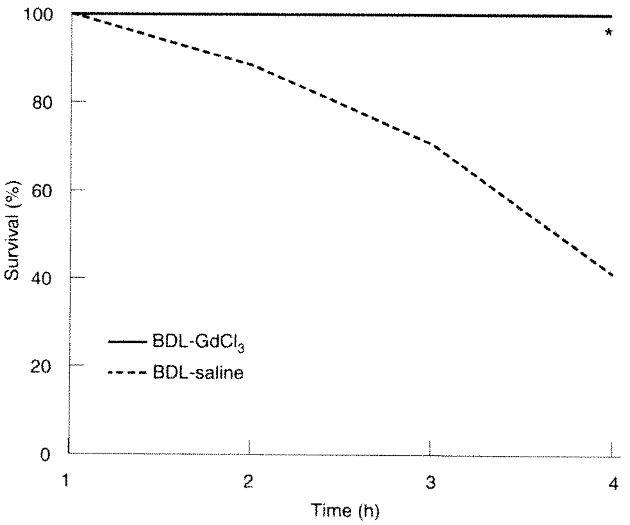

Fig. 2 Effect of Kupffer cell blockade with gadolinium chloride ($GdCl_3$) on survival of bile duct-ligated (BDL) animals after intraperitoneal injection of endotoxin 0·02 mg per 100 g.

TNF secretion

Using low-dose endotoxin (0·0002 mg per 100 g), the peak plasma TNF response to intraperitoneal endotoxin at 1 h

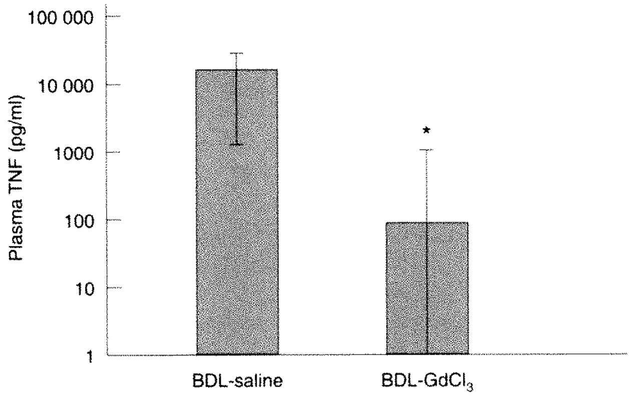

Fig. 3 Effect of Kupffer cell blockade with gadolinium chloride ($GdCl_3$) on plasma tumour necrosis factor (TNF) levels in bile duct-ligated (BDL) animals 1 h after intraperitoneal injection of endotoxin 0·0002 mg per 100 g. $^*P = 0{\cdot}002$ *versus* BDL-saline (Mann–Whitney *U* test)

was significantly diminished by pretreatment with gadolinium chloride (BDL-$GdCl_3$ 88 (i.q.r. 0–1065) pg/ml *versus* BDL-saline 16 550 (i.q.r. 1255–29 360) pg/ml; $P = 0{\cdot}002$) (*Fig. 3*).

Kupffer cell population

Histological examination of liver sections confirmed significant depletion of Kupffer cells in jaundiced animals pretreated with gadolinium chloride (median Kupffer cell count for BDL-$GdCl_3$ 35 (i.q.r. 26–43) per h.p.f. *versus* BDL-saline 65 (i.q.r. 55–88) per h.p.f.; $P < 0{\cdot}0001$).

Discussion

Using *in situ* hepatic perfusion, the authors have previously demonstrated impaired endocyte function and hypersecretion of cytokines by the Kupffer cell population in experimental obstructive jaundice *in vitro*[5]. The objective of this series of experiments was to assess the significance of these findings *in vivo*. Intraperitoneal administration of endotoxin was used as a simple, easily reproducible, means of Kupffer cell stimulation, simulating the 'shower' of intestinal derived endotoxin that may follow biliary manipulation in patients with extrahepatic obstructive jaundice. The doses of endotoxin used in these studies were based on preliminary studies with this model.

In experiment 1, jaundiced animals were highly sensitive to exogenous endotoxin compared with sham-operated controls. Reduction of the dose of endotoxin by a factor of 10 000 was required to achieve a survival rate in BDL animals similar to that of sham-operated animals at 4 h. High sensitivity to endotoxin administered both orally (following sensitization with lead acetate) and parenterally has been recognized for some time in rats after BDL[8,9]. However, investigations into the pathophysiology of this response to date have concentrated largely on alterations in mononuclear phagocytic function.

Plasma TNF levels peaked 1 h after exposure to endotoxin in jaundiced and sham-operated animals. TNF secretion by jaundiced animals exceeded that by sham animals by a factor of approximately 100. The kinetics of this response are in keeping with previous studies in septic models; however, the magnitude is clearly greater in animals following BDL[10].

Selective blockade of the Kupffer cell population by gadolinium chloride is a well recognized technique of studying Kupffer cell function. In this study, survival after administration of endotoxin was significantly improved by preadministration of gadolinium chloride. Kupffer cell blockade also attenuated the systemic TNF response to exogenous endotoxin. Although a number of cell types may contribute to the systemic TNF response to endotoxin, the findings using gadolinium chloride suggest that Kupffer cells are the major source of systemic TNF in this experimental model of obstructive jaundice *in vivo*.

The mechanism of action of gadolinium chloride is not fully understood. Initial studies suggested gadolinium chloride interfered with surface attachment and engulfment of test probes[11]. More recent studies using immunohistochemical techniques have demonstrated Kupffer cell depletion 48 h after parenteral administration of gadolinium chloride[12]. It was proposed that, following Kupffer cell uptake of gadolinium chloride, gadolinium ions were released in the acidic environment of the lysosome and resulted in selective Kupffer cell toxicity. This may result in global blockade of Kupffer cell function without microscopic ablation of the total Kupffer cell population and may explain the disparity between the reduction in Kupffer cell counts (50 per cent) and the magnitude of the suppression of TNF secretion in animals given gadolinium chloride in this study. Gadolinium chloride itself may alter hepatic cytokine activity. Rai *et al.*[13] have reported that gadolinium chloride attenuated hepatic expression of anti-inflammatory IL-10 but increased expression of TNF in rats following partial hepatectomy. Conversely, Louis *et al.*[14] found that pretreatment with gadolinium chloride increased serum IL-10 concentration and decreased TNF levels following galactosamine–lipopolysaccharide-induced liver injury in mice. The significance of these findings in the present model is uncertain as the effects of biliary obstruction on hepatic IL-10 levels are unknown.

The mechanisms underlying the upregulation of Kupffer cell secretory function in this model of biliary obstruction have not been elucidated in this study. There is evidence of both an increase in Kupffer cell number in the liver following BDL and a phenotypic shift in favour of augmented expression of the putative endotoxin receptor CD14[15–17]. However, these findings alone are unlikely to account for magnitude of the increase in secretory response demonstrated in this study.

In conclusion, these data support the view that increased secretion of TNF by the Kupffer cell population is a critical feature of the response to endotoxin in experimental obstructive jaundice. If confirmed in clinical studies, they suggest a potential benefit from immunological or pharmacological therapies to attenuate excessive cytokine secretion, which could be administered before diagnostic or therapeutic intervention in patients with obstructive jaundice.

Acknowledgements

J.A.K. was in receipt of a British United Provident Association Research Fellowship awarded by the Royal College of Surgeons of England.

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Original article

Value of percutaneous transhepatic portography before hepatectomy for hilar cholangiocarcinoma

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Background: The diagnostic value of percutaneous transhepatic portography (PTP) for assessing cancer invasion of the portal bifurcation in patients with hilar cholangiocarcinoma has not been studied previously.
Methods: From April 1977 to March 1998 combined hepatobiliary and portal vein resection was performed in 45 patients. In 25 patients, PTP was carried out before operation and the resected portal bifurcation was examined histologically. Correlation between portographic and microscopic findings at the portal bifurcation was studied retrospectively.
Results: Portographic and microscopic findings were classified into three groups (type A, B or C, and grade 0, I or II respectively) according to the findings at the portal bifurcation. There was a significant correlation between the portographic type and degree of cancer invasion ($P = 0.0001$). In seven of the eight patients with type A portograms, there was no microscopic cancer invasion of the portal bifurcation. In 15 of the 17 patients with type B or C portograms, cancer invasion was found microscopically. All patients with microscopic grade II invasion had type C portograms.
Conclusion: PTP can be used to evaluate cancer invasion of the portal bifurcation with sufficient reliability for preoperative staging of hilar cholangiocarcinoma.

Paper accepted 5 July 1999

British Journal of Surgery 1999, 86, 1415–1421

Introduction

Surgical resection is the best therapeutic strategy for patients with hilar cholangiocarcinoma. Recently, liver resection has become more popular for treating this intractable disease because of the possibility of achieving a tumour-free resection margin and a better long-term survival compared with local resection[1–13]. Hilar cholangiocarcinoma often invades the vascular structures in the hepatoduodenal ligament. Such findings make resection and reconstruction more complicated. Despite the difficulty of surgery for advanced carcinoma, several authors have reported the clinical utility of hepatectomy with combined resection of the portal vein and/or hepatic artery using vascular surgical techniques to achieve curative resection[14–19].

A retrospective study was carried out to determine the value of percutaneous transhepatic portography (PTP) before liver resection in the assessment of cancer invasion of the portal vein in patients with hilar cholangiocarcinoma.

Patients and methods

From April 1977 to March 1998, 145 patients with hilar cholangiocarcinoma underwent liver resection with ($n = 45$) or without ($n = 100$) portal vein resection and reconstruction at the First Department of Surgery, Nagoya University Hospital. Of the 45 patients with portal vein resection, preoperative PTP was performed in 31 patients, conventional arterial portography in 12 and trans-splenic portography in two. Of the 31 patients who had PTP, six were excluded because PTP provided insufficient detail of the portal bifurcation (two patients), biliary surgery had been performed previously (two) or the resected portal bifurcation could not be examined histologically (two). The remaining 25 patients were enrolled in the study. In addition, all patients underwent preoperative ultrasonography and computed tomography with enhancement. There were 18 men and seven women with a mean(s.d.) age of 59·0(10·5) (range 33–77) years. No patient was cirrhotic. Jaundice on admission was present in 21 patients. No jaundice and/or cholangitis was observed at the time of operation as patients had been treated with percutaneous transhepatic biliary drainage to prevent postoperative hepatic failure with or without septic complications[20–25]. Major hepatectomy with *en bloc* resection of the caudate lobe, portal vein resection and reconstruction, and extrahepatic bile duct resection was performed in all 25 patients (*Table 1*). A combined pancreatoduodenectomy was performed in two patients with cancer infiltration of the intrapancreatic bile duct[26].

For PTP, a 5-Fr catheter was advanced into the superior mesenteric vein under fluoroscopic control through a catheter sheath introduced by ultrasonographically guided puncture of the right anterior portal vein or the umbilical portion of the left portal vein. Before October 1994, PTP was obtained using a conventional angiography system (Toshiba KXO-1250C; Toshiba, Tokyo, Japan). Thereafter, a digital subtraction system (Toshiba KXO-80) was used. The total dose of contrast medium administered (Iopamiron; Schering, Berlin, Germany) was 20 ml (injection rate 10 ml/s) in the former period, and 10 ml (injection rate 5 ml/s) in the latter period. Portograms were taken in anteroposterior and right anterior oblique projections. Right anterior cranial oblique, right anterior caudal oblique or lateral projections were also obtained as needed. The image intensifier was tilted 30° to the patient's right for the right anterior oblique projection, 30° to the patient's right and 20° cranial for the right anterior cranial oblique projection, and 30° to the patient's right and 20° caudal for the right anterior caudal projection. Portographic

Table 1 Operative procedures performed in 25 patients

Procedure	No. of patients
Left hepatic lobectomy + caudate lobectomy	4
Extended left hepatic lobectomy + caudate lobectomy	4
Left hepatic trisegmentectomy + caudate lobectomy	3
Right hepatic lobectomy + caudate lobectomy	2 (1)
Extended right hepatic lobectomy + caudate lobectomy	8 (1)
Right hepatic trisegmentectomy + caudate lobectomy	4

Values in parentheses are patients having pylorus-preserving pancreatoduodenectomy

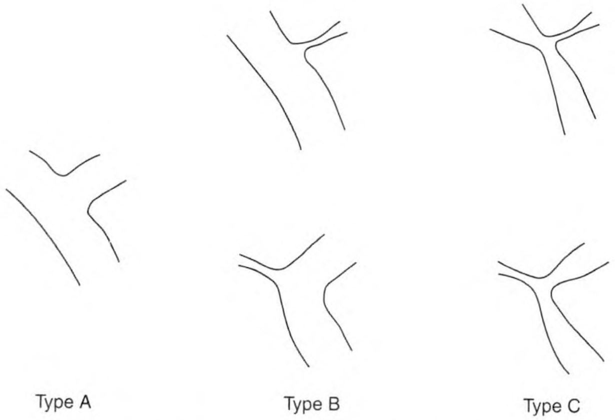
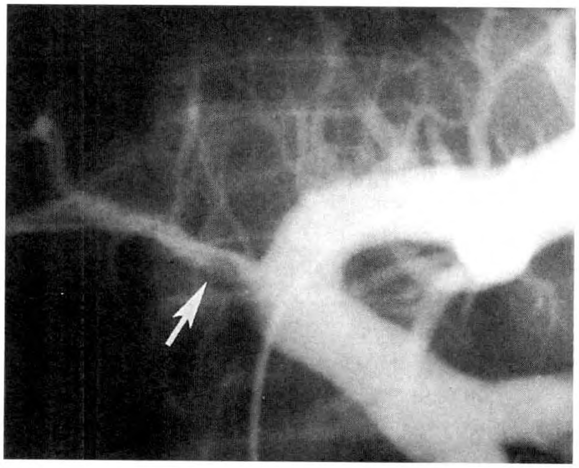
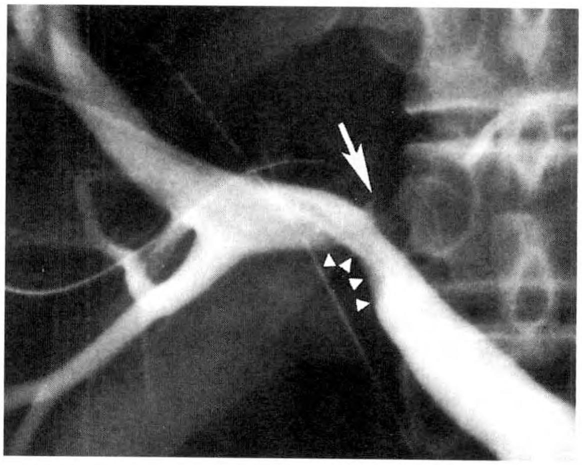


Fig. 1 Illustrations of the portographic findings at the portal bifurcation. Type A, no abnormal findings. Type B, stenosis or obstruction at the origin of the right or the left portal vein. Type C, narrowing of the portal vein on the contralateral side of the origin of the involved right or left portal vein

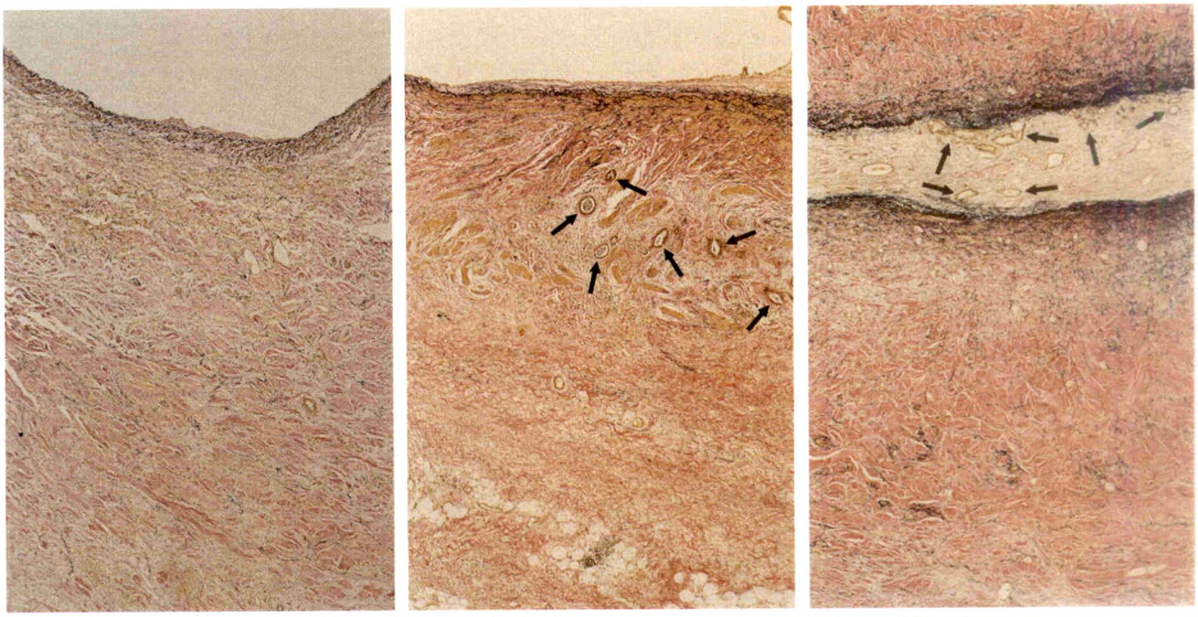


a Right portal vein stenosis (type B)



b Left portal vein obstruction (type C)

Fig. 2 Preoperative percutaneous transhepatic portography. **a** Type B: stenosis is observed at the origin of the right portal vein (arrow); the right posterior portal branch is not visualized. **b** Type C: the left portal vein is obstructed at the bifurcation (arrow); narrowing is observed on the contralateral side of the involved left portal vein (arrowheads)



a No invasion **b** Grade I invasion **c** Grade II invasion

Fig. 3 Photomicrographs of the portal bifurcation (elastic fibre van Gieson stain, original magnification × 27).
a Grade 0, no cancer invasion.
b Grade I, cancer invasion limited within the tunica adventitia or media (arrows).
c Grade II, cancer invasion reaching the tunica intima (arrows)

findings were divided into three types (*Fig. 1*): type A had no abnormal findings ($n=8$), type B showed stenosis or obstruction at the origin of either the right or the left portal vein ($n=8$) (*Fig. 2a*) and type C exhibited narrowing at the contralateral side of the involved vein ($n=9$) (*Fig. 2b*). In nine patients without marked stenosis or obstruction of the right portal vein who were to undergo right hepatic lobectomy or more extensive liver resection, portal vein embolization[22,27–29] was carried out after PTP. There were no procedure-related complications.

After performing cholangiography on the resected specimen, the extrahepatic bile duct was opened longitudinally from the distal resection margin to the proximal margin. The gross tumour type was assessed as papillary, nodular, nodular infiltrating or diffusely infiltrating[30,31]. The specimens were fixed in 10 per cent formalin for several days and serially sectioned at 5-mm intervals. The specimens were prepared in the usual manner for microscopic examination using haematoxylin and eosin and elastic fibre van Gieson stains. Microscopic tumour invasion of the portal bifurcation was classified as grade 0 (no cancer invasion) (*Fig. 3a*), grade I (cancer invasion limited to the tunica adventitia or media) (*Fig. 3b*) or grade II (cancer invasion reaching the tunica intima) (*Fig. 3c*).

Statistical analysis was carried out with Spearman's rank correlation test. Survival rates were determined by the Kaplan–Meier method, and differences were analysed by the generalized Wilcoxon test. $P<0{\cdot}05$ was considered statistically significant.

Results

The gross tumour type was papillary ($n=1$), nodular infiltrating ($n=5$) or diffusely infiltrating ($n=19$)[30,31]; thus 24 of the 25 patients had an infiltrating tumour. There was no association between the portographic findings and gross tumour type. On the other hand, a significant ($P=0{\cdot}0001$) association was found between portographic findings and the microscopic grades of cancer invasion (*Table 2*). In seven of the eight patients with type A portograms, there was no

Table 2 Correlation between portographic findings and microscopic carcinoma invasion of the portal bifurcation

	Microscopic invasion		
Portographic type	Grade 0	Grade I	Grade II
A	7	1	0
B	2	6	0
C	0	5	4

$r_S=0{\cdot}793$, $P=0{\cdot}0001$

microscopic cancer invasion of the portal bifurcation. In 15 of the 17 patients with type B or C portograms, there was cancer invasion. All patients with microscopic grade II invasion had type C portograms. In contrast, the diagnostic abilities of ultrasonography and computed tomography were low. Of 16 patients with microscopic grade I or II invasion, invasion was detected with ultrasonography in only three and with computed tomography in five. Moreover, these modalities did not allow discrimination between grade I and II invasion.

Despite a lack of microscopic cancer invasion of the portal bifurcation, seven of the eight patients with type A portograms eventually underwent combined portal vein resection. In one patient, marked autonomic nerve invasion around the portal bifurcation was found. In the two patients who underwent right hepatic trisegmentectomy with caudate lobectomy, the transverse portion of the left portal vein distal to the portal bifurcation was involved (*Fig. 4*). In the remaining four patients, cancer invasion was suspected macroscopically during operation. Although cancer did not microscopically invade the portal bifurcation in these four patients, cancer invasion together with marked fibrosis was observed close to the dissection margins (*Fig. 5*).

Resection procedures of the portal vein were recorded according to the portographic findings and type of hepatectomy (*Table 3*). Because the transverse portion of the left portal vein is long compared with the right portal trunk, segmental resection and reconstruction is much easier to perform with right-sided than with left-sided hepatectomy. Therefore, irrespective of the portographic findings, segmental resection was more common with right-sided hepatectomy. In contrast, wedge resection was more common with left-sided hepatectomy. However, segmental resection was mandatory in eight of nine patients with type C portograms. Although the remaining patient underwent wedge resection for technical reasons, the postresection defect in the portal vein was large. The vein was therefore reconstructed with a patch graft using saphenous vein.

There were no postoperative complications related directly to portal vein resection and reconstruction. Hospital death was observed in only one patient who underwent left hepatic lobectomy, caudate lobectomy, distal gastrectomy for associated gastric tumour, and had portal vein and right hepatic artery resection and reconstruction. This patient died from sepsis resulting from leakage of gastroduodenostomy 95 days after operation, giving a mortality rate of 4 per cent (one of 25 patients). The 1-, 3- and 5-year survival rates for the 25 patients were 15, three and one respectively, and the median survival was 18·1 months. Survival was significantly ($P<0{\cdot}001$) better than that of 38 patients with irresectable hilar cholangiocarcinoma treated at the authors' hospital during the same time period (*Fig. 6*).

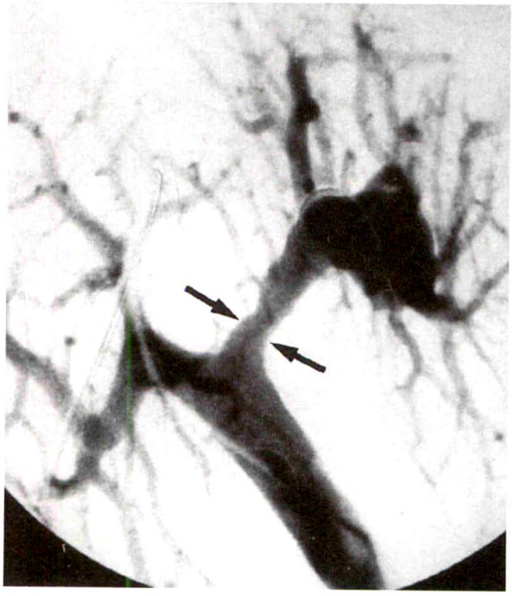


Fig. 4 Lateral view of preoperative percutaneous transhepatic portography. The proximal margin of the stenosis of the left portal vein is clearly demonstrated (arrows). The portal bifurcation is intact. Segmental excision of the portal vein was performed because right hepatic trisegmentectomy was required for removal of the tumour. The degree of microscopic cancer invasion of the portal bifurcation was classified as grade 0

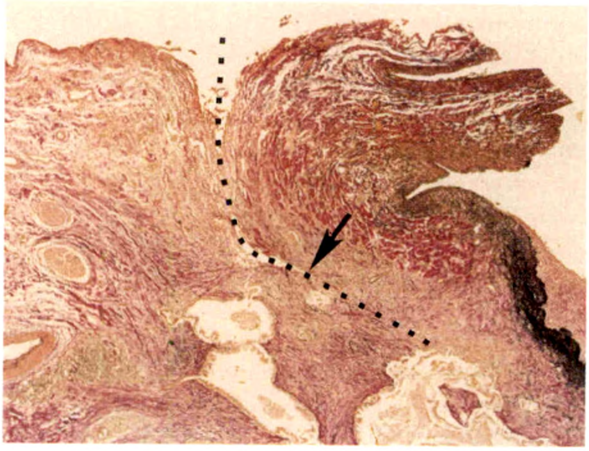
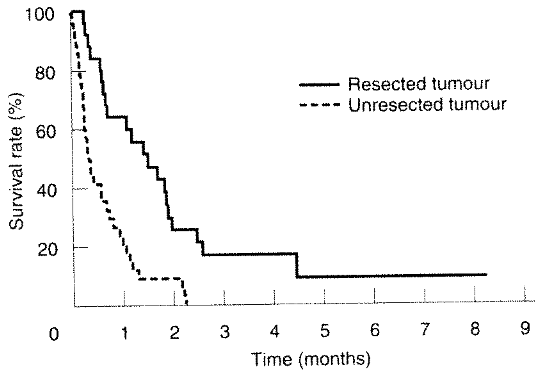


Fig. 5 Photomicrograph of the portal bifurcation (elastic fibre van Gieson stain, original magnification × 17). Cancer does not invade the adventitia of the portal vein. However, cancer and severe fibrosis are close to the wall of the portal bifurcation. Dissection was avoided to achieve a negative transection plane (arrow). The dotted line indicates the estimated dissection plane in case of hepatobiliary resection without portal vein resection

Table 3 Relationship between portographic findings and resection type of the portal vein

	Portographic type			
Resection type	A	B	C	Total
Right-sided hepatectomy				
Segmental excision	5	3	4	12
Wedge resection	1	1	0	2
Left-sided hepatectomy				
Segmental excision	0	1	4	5
Wedge resection	2	3	1	6



No. at risk									
Resected	25	15	6	3	2	1	1	1	1
Unresected	38	9	3	0	0	0	0	0	0

Fig. 6 Survival curves for the 25 patients in the present study and for 38 patients with irresectable hilar cholangiocarcinoma. $P < 0.001$ (Wilcoxon test)

Discussion

Computed tomography and ultrasonography have been used to assess extramural extension of cholangiocarcinoma. However, these examinations have limited diagnostic utility for cancer invasion of the portal vein, as was also found in the present study. Arterial portography has also been widely used for this purpose, but is of less value because it rarely demonstrates the portal bifurcation clearly owing to insufficient opacification and/or superimposition of the portal branches[32,33]. In the authors' experience, arterial portography rarely allowed a correct preoperative diagnosis of cancer invasion of the portal bifurcation (data not shown). On the other hand, PTP may be used to obtain high-quality portograms which can be used to make a precise diagnosis. In addition, the recent advent of digital subtraction angiography has reduced the volume of contrast medium required. In the present series, using digital subtraction angiography, only 10 ml of contrast medium was required per portogram, allowing for two or more projections. Overall, PTP is safe, easy to perform, and can produce high-quality portograms in several projections. These advantages outweigh the disadvantage of the invasive nature of the procedure.

Hilar cholangiocarcinoma often infiltrates extramurally and invades adjacent blood vessels[34,35]. The infiltration pattern of cholangiocarcinoma is closely related to the gross tumour type[36]. The present authors have previously reported that submucosal extension at the proximal border of hilar cholangiocarcinoma is characteristic of nodular infiltrating or diffusely infiltrating tumours[31]. The present study also demonstrated that, with few exceptions, cholangiocarcinoma with portal vein invasion is associated with nodular infiltrating or diffusely infiltrating tumours. This indicates that the gross tumour type should be considered when portal vein invasion is suspected. A careful search for the findings of rigidity, tapering or narrowing of the bile duct wall on cholangiography may lead to an accurate preoperative diagnosis of the gross tumour type.

The most important finding arising from the present study is the close association between portographic findings and the microscopic grade of cancer invasion. In 15 of the 17 patients with type B or C portograms, microscopic cancer invasion of the portal bifurcation was observed. This clearly demonstrates that portal vein resection and reconstruction is essential when the portogram shows a stenosis or obstruction at the origin of either the right or the left portal vein. Moreover, all patients with microscopic grade II invasion had type C portograms, and eight of the nine with type C portograms eventually underwent segmental resection of the portal vein. In the remaining patient with a type C portogram, who underwent wedge resection, the post-resection defect of the vein was large and patch graft with autogenous vein was used for reconstruction. These findings are important from the surgical viewpoint. Portographic findings of contralateral narrowing of the involved portal vein imply marked cancer invasion. Therefore, segmental resection, not wedge resection, should be performed. PTP taken in two or more projections clearly demonstrates tumour extension along the portal vein, which makes it possible to estimate the part and the length of the portal vein to be resected and, in turn, to design the resection and reconstruction procedure in detail.

Despite a lack of abnormal portographic findings, four patients eventually underwent portal vein resection because cancer invasion was suspected macroscopically during operation. Microscopic examination revealed cancer infiltration with marked fibrosis extended near the resection margins. Without portal vein resection, the dissection plane would have been positive (*Fig. 5*). In these patients, portal vein invasion was microscopically negative, but could have been surgically positive. Such conditions are hard to detect with PTP, and represent a limitation of the diagnostic utility of the technique. Kaneko *et al.*[37] have emphasized that intraportal endovascular ultrasonography provides accurate information regarding portal vein invasion in patients with pancreatobiliary carcinoma; however, it was difficult to differentiate between cancer invasion and severe inflammation. Furthermore, in view of the results of the present study, even if no cancer invasion of the portal bifurcation is demonstrated on diagnostic imaging, portal vein resection is recommended in patients with surgically positive portal vein invasion.

Launois *et al.*[38] have reported that the main reason for irresectability of cholangiocarcinoma is invasion of the portal bifurcation. Hoevels and Ihse[32] have stressed that portography showing portal vein invasion indicates irresectability of bile duct carcinoma. However, such a concept has become antiquated. Recently, several surgeons have described portal vein resection for advanced biliary tract carcinoma and have advocated an aggressive surgical strategy[14–19]. So far, the present authors have also performed combined hepatobiliary and portal vein resection in patients with advanced hilar cholangiocarcinoma[18]. In this series, the mortality rate was low (only one of 25 patients) and the survival rate was unexpectedly improved, with three 3-year survivors. Now, the presence of portal vein invasion is not a contraindication for surgical resection in patients with hilar cholangiocarcinoma. PTP can be used to evaluate cancer invasion of the portal bifurcation with sufficient reliability for preoperative staging of hilar cholangiocarcinoma.

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Original article

Comparison of intra-arterial digital subtraction angiography, magnetic resonance angiography and duplex ultrasonography for measuring carotid artery stenosis

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Background: Duplex ultrasonography and magnetic resonance angiography (MRA) are becoming competitive alternatives to angiography for determining the degree of internal carotid artery (ICA) stenosis. Varying reports have been published regarding the suitability of each technique for grading ICA disease. This retrospective study compared the merits of these three modalities for measuring ICA stenosis.

Methods: One hundred and eleven patients being considered for carotid endarterectomy underwent intra-arterial digital subtraction angiography (DSA) via arch injection. Duplex imaging was performed in all patients and MRA in 50. The degree of carotid stenosis estimated by the three modalities was compared.

Results: There was good correlation between subjectively graded MRA and DSA images ($r = 0{\cdot}87$, $P < 0{\cdot}001$, $n = 82$ carotids) but poor correlation for objective estimates. MRA tended to underestimate the degree of stenosis (bias $-4{\cdot}5$ per cent) compared with DSA, but showed good correlation with duplex ultrasonography estimates ($r = 0{\cdot}86$, $P < 0{\cdot}001$, $n = 87$ carotids). Both non-invasive modalities produced high values of sensitivity and specificity in estimating stenoses of greater than 70 per cent. MRA was less sensitive for distinguishing between severe stenosis and complete occlusion.

Conclusion: This study did not resolve the debate regarding the method of choice as both MRA and duplex ultrasonography were accurate for imaging carotid stenoses.

Paper accepted 24 June 1999

British Journal of Surgery 1999, **86**, 1422–1426

Introduction

Carotid endarterectomy is now advocated for symptomatic patients with an internal carotid artery (ICA) stenosis causing a reduction in luminal diameter of 70–99 per cent[1,2]. Angiography has been used to determine the degree of ICA stenosis, but is associated with a 1–2 per cent stroke rate, and reports on its accuracy and reproducibility are conflicting[3–5]. The problems associated with digital subtraction angiography (DSA) have encouraged the use of alternative imaging modalities such as duplex ultrasonography and magnetic resonance angiography (MRA), which are now used in many institutions to select patients for carotid surgery[6].

Comparison with conventional angiography has demonstrated high sensitivities and κ values for identifying ICA stenoses of greater than 50 per cent using duplex ultrasonography[7,8] and a high level of accuracy using three-dimensional time-of-flight (3D-TOF) MRA[6]. However, there remains controversy regarding the relative merits of these tests for selecting patients for surgery[6,9,10]. The disparity between these studies may reflect the fact that the diagnostic results are dependent on many factors such as the equipment used, operator experience and diagnostic criteria.

An imaging modality used to select patients for carotid surgery should be able to measure the ICA diameter stenosis, length of the lesion and provide calibre measurements of the distal, cervical ICA. At this hospital, information about the intracranial circulation has not influenced patient management. The present study investigated the interobserver variability for reading intra-arterial DSA by arch injection and MRA images both subjectively and objectively. Also compared were the accuracies of MRA and duplex ultrasonography relative to DSA for selecting patients for carotid surgery based on the information described above.

Patients and methods

Some 111 patients who underwent intra-arterial DSA were entered into this study. There were 74 men and 37 women with a mean(s.d.) age of 65(7) (range 45–78) years. Intra-arterial DSA was performed using a 4-Fr pigtail catheter from a femoral approach. A posterior–anterior view of the head was followed by a left anterior–oblique arch injection that included the carotid bifurcations. This view was supplemented by two further oblique orthogonal projections with the head turned to each side. These were optimized to prevent vessel overlap, but if this occurred a further projection or projections were obtained.

Duplex ultrasonographic imaging was performed in all 111 patients using an ultrasound colour flow mapping system (7-MHz linear array transducer 128xP/10v; Acuson, Mountain View, California, USA). The degree of internal carotid stenosis was graded using conventional duplex criteria as described previously[11].

MRA was performed in 50 patients who gave informed consent; some of the above patients had surgery before an MRA study could be performed. 3D-TOF MRA was performed on a 1·5-T system (Philips Gyroscan, S15/ACS R3.6.3; Philips Medical Systems, Best, The Netherlands). The MRA sequence was flow-compensated and used saturation pulses to eliminate the signal from venous flow.

Data analysis

Angiographic images were assessed independently by two radiologists. First, on hard-copy digital subtraction angiograms, the percentage ICA stenosis was graded subjectively in 5 per cent increments. This involved an estimate of percentage stenosis using the distal ICA lumen diameter as a reference. Reconstructed MRA images were processed using a maximum intensity projection algorithm and images displayed at 15° intervals for subjective evaluation of stenosis diameter. Second, images were transferred to an image analysis workstation (Philips Easy Vision) and assessed objectively using electronic screen callipers (resolution 0·1 mm). Measurements were obtained by moving the screen cursor to the perceived edges of the vessel wall at the maximum point of ICA stenosis and at the point where the distal ICA walls became parallel. The percentage diameter stenosis was then computed based on the North American Symptomatic Carotid Endarterectomy Trial criteria[1]. The computed measurements of stenosis were not made available to the observer to avoid bias. MRA images that showed a discrete region of signal dropout in the ICA, indicating a severe stenosis, were arbitrarily classified as having a stenosis of greater than 95 per cent.

Kendall's rank correlation was used to investigate any bias in comparisons related to stenosis size. Linear regression was used to determine the relationship between stenosis estimates, and difference of means analysis for comparing agreement between stenosis estimates by the different modalities. κ statistics were used to assess the agreement between multicategorical data.

Results

A total of 222 carotid bifurcations from the 111 patients were available for this study. No patient suffered any neurological event during or after any of the imaging modalities investigated. Six (3 per cent) of 222 DSA images and 13 of 100 MRA images were non-diagnostic owing to poor image quality. Non-diagnostic MRA scans contained imaging artefacts caused by patient movement ($n=8$) or dental prostheses ($n=1$). The remaining four patients were imaged in the early part of the series and inaccurate planning resulted in insufficient coverage of the carotid bifurcation. All duplex ultrasonographic scans were considered diagnostic.

Interobserver variability

High correlation coefficients were found between the two observers for both the objective and subjective estimates of stenosis on DSA (216 carotids); the subjective method produced slightly higher correlation values However, difference of means analysis showed slightly wider limits of agreement for the objective (−32 to +49 per cent) compared with the subjective measurements (−30 to +45 per cent). In a subset of the MRA images the two observers' analyses showed the limits of agreements to be much wider for the objective method (−67 to +54 per cent; 51 carotids) than for the subjective assessment (−28 to +18 per cent; 53 carotids) (*Table 1*).

Multimodality comparison

Comparison of subjective estimates of stenosis by MRA and DSA showed good correlation with the subjectively analysed data ($r=0{\cdot}87$, $P<0{\cdot}001$, $n=82$) but poorer correlation with objectively analysed data ($r=0{\cdot}60$, $P<0{\cdot}001$, $n=82$). Correlation and agreement values comparing the three imaging modalities (using subjective stenosis estimates) are summarized in *Table 1*. All three modalities correlated well with each other. The plots of duplex ultrasonography *versus* DSA findings, and MRA *versus* DSA results demonstrated a high degree of correlation (r = 0·86, P < 0·001, n = 216 and r = 0·87, P < 0·001, n = 82 respectively) (*Figs 1* and *2*). However, difference of means analysis (*Table 1*) revealed a tendency for MRA to underestimate stenosis diameter (bias −4·5 per cent), while the limits of agreement showed differences between DSA and ultrasonography of −35 to + 29 per cent compared with −38 to + 29 per cent for DSA and MRA.

Degree of stenosis estimated by ultrasonography and MRA showed good correlation (r = 0·86, P < 0·001, n = 87 carotids) while difference of means analysis demonstrated no significant bias between MRA and ultrasonography

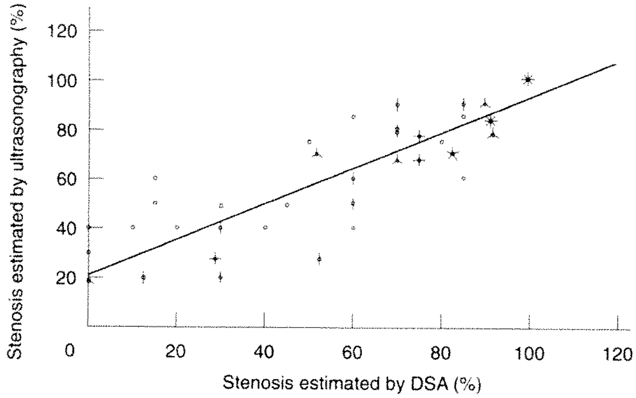

Fig. 1 Estimates of internal carotid artery stenosis by duplex ultrasonography *versus* stenosis graded subjectively by digital subtraction angiography (DSA). Multiple data points are represented as petals (r = 0·86, P < 0·001, n = 216)

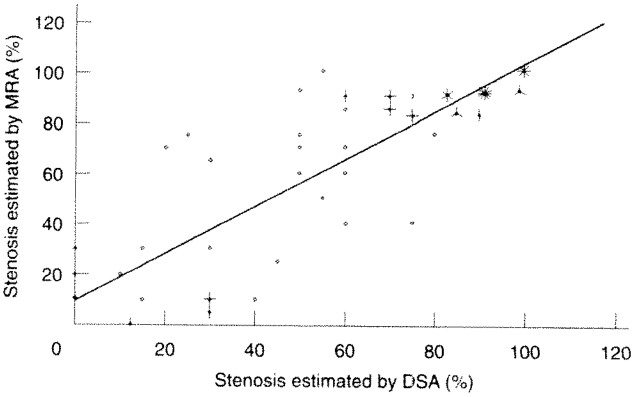

Fig. 2 Subjectively graded three-dimensional magnetic resonance angiography (MRA) *versus* subjectively graded digital subtraction angiography (DSA) estimates of internal carotid artery stenosis. Multiple data points are represented as petals (r = 0·87, P < 0·001, n = 82)

Table 1 Comparison of internal carotid stenosis estimates by digital subtraction angiography, duplex ultrasonography and three-dimensional magnetic resonance angiography

	r	*n*	Bias (%)	Confidence intervals (%)	Kappa
Reproducibility					
3D MRA objective	0·62	51	−6·3	−67 to +54	—
3D MRA subjective	0·94	53	−4·7	−28 to +18	—
Multimodality*					
DSA *versus* 3D MRA	0·87	82	−4·5	−38 to +29	0·76
DSA *versus* duplex	0·88	216	−2·8	−35 to +29	0·81
Duplex *versus* 3D MRA	0·86	87	−1·6	−38 to +35	0·72

*Subjective estimates by digital subtraction angiography (DSA) and three-dimensional magnetic resonance angiography (3D MRA). *r*, Summary of correlation coefficients; *n*, number of comparisons; difference of means analysis (bias and confidence intervals)

Table 2 Sensitivity and specificity for detecting internal carotid artery stenoses of greater than 70 per cent and occlusions using digital subtraction angiography as the gold standard

		Stenosis > 70%		Occlusion	
Comparison	*n*	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Duplex *versus* DSA	216	94	84	96	99
3D MRA *versus* DSA	82	98	72	70	99

DSA, digital subtraction angiography; 3D MRA, three-dimensional magnetic resonance angiography

(*Table 1*). The agreement limits for these two methods were wide and indicated that values could differ between the two methods by as much as 38 per cent.

Decision matrices were used to determine the sensitivity and specificity first for identifying patients with an ICA stenosis of greater than 70 per cent and second for identifying an occluded ICA (*Table 2*). Duplex imaging and MRA produced high values of both sensitivity and specificity for estimating stenoses of greater or less than 70 per cent diameter reduction. MRA had reduced sensitivity for distinguishing between severe stenosis and complete occlusion compared with duplex imaging.

Discussion

The results of this study support previous findings that subjective evaluation of the degree of stenosis of the ICA by intra-arterial DSA produced better agreement and correlation than objective estimates, even in the presence of artefacts from calcification, overlying vessels or poor-quality images[11]. This finding has now been extrapolated to MRA, where subjectively assessed 3D-TOF images also provided the highest interobserver agreement.

Other investigators have reported good interobserver and intraobserver variability for grading stenoses objectively from carotid arteriograms, and good correlation between objective and subjective estimation of carotid stenoses ($r = 0{\cdot}91$)[3,5]. In the present study this level of agreement was not reproduced. The image quality of MRA was inferior to that of DSA. There were further problems with interpretation of magnetic resonance angiograms due to short segment scans, imperfect background saturation and signal loss in vessels containing turbulence (*Fig. 3*). Signal loss can be attributed to a number of factors, including intravoxel dephasing and complex flow patterns. 3D-TOF MRA, with its high spatial resolution and short echo times, is more resistant to such causes of signal loss, so that velocity will be the most significant factor causing a signal void at a stenosis[12]. Subjective evaluation enabled the angiogram reporter to allow for such shortcomings, but objective measurements were not possible when the vessel walls could not be identified precisely.

The high sensitivity and specificity achieved by MRA and duplex imaging in this study suggests that, if stenosis diameter alone is the most important factor, either modality could be used. Other factors that should be considered when selecting an investigation to measure carotid stenosis include the rate of non-diagnostic scans, cost and the ability to provide other useful information such as lesion length, vessel calibre, plaque characterization, intracranial vessel anatomy and the presence of proximal stenoses. At present there are no validated techniques to provide information on plaque morphology. The significance of intracranial disease is controversial[13,14], while proximal common carotid disease is rare, occurring in just 1·8 per cent in a review of 1000 arch angiograms[15]. Duplex imaging is capable of achieving most of the above, while MRA is associated with a high non-diagnostic scan rate (13 per cent) and a higher cost.

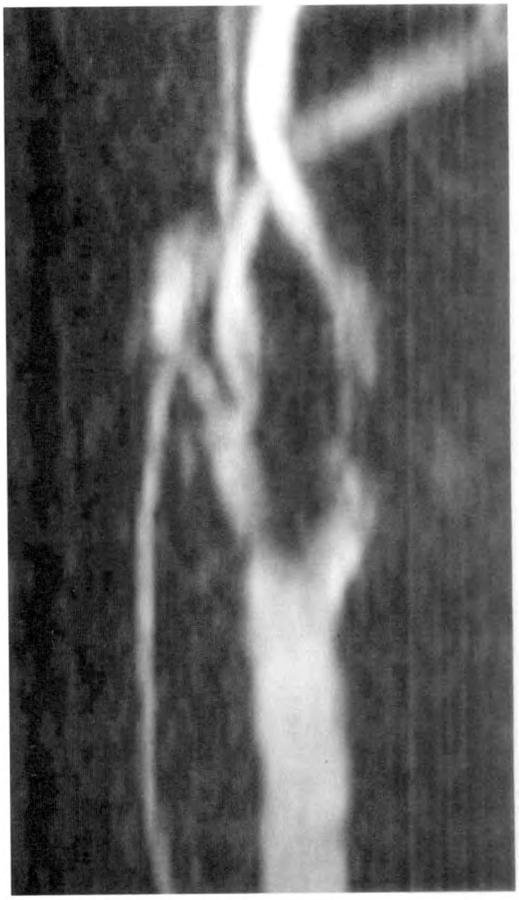

Fig. 3 Three-dimensional magnetic resonance angiogram of a carotid bifurcation showing signal loss due to turbulence

In many centres duplex ultrasonography is the main imaging method before operation. Where ultrasonography fails or is ambiguous, such as in the case of heavily calcified vessels or subocclusion, then DSA is used. The MRA images obtained in this study were less sensitive in distinguishing between critical stenosis and complete occlusion than duplex ultrasonography. Recent technical advances in MRA have produced improvements in flow imaging and scan duration that may resolve these problems[16]. First-pass, contrast-enhanced MRA has become widely accepted for abdominal and peripheral vascular imaging, although its application to carotid angiography has been delayed owing to greater resolution demands[17]. Recently, improved results with gadolinium-enhanced MRA have been described[18].

This study did not resolve the debate regarding the method of imaging patients before carotid surgery. Both non-invasive imaging by MRA and duplex ultrasonography can provide accurate initial imaging of carotid stenoses; DSA can be used selectively in patients in whom the initial test is ambiguous.

Acknowledgements

This work was funded by The Stroke Association and The Special Trustees of Guy's and St Thomas' Hospitals.

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Original article

Role of nitric oxide in intestinal ischaemia-reperfusion injury studied using electron paramagnetic resonance

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Background: The role of nitric oxide in intestinal ischaemia–reperfusion (I/R) remains poorly defined, partly because of difficulty in detecting the nitric oxide free radical. In this study nitric oxide production was assessed during intestinal I/R by direct measurement using electron paramagnetic resonance (EPR), and the production of nitric oxide in jejunum and ileum was correlated with their different abilities to resist I/R injury.

Methods: Rats were given an electron spin trapper (diethyldithiocarbamate/ferrous citrate) by intraperitoneal injection. Thirty-six segments each of jejunum and ileum were subjected to 15–90 min of ischaemia and 25 min of reperfusion. Tissue samples were analysed for EPR signals using a spectrometer.

Results: Mean(s.d.) basal nitric oxide level was significantly higher in ileum (3·39(1·42) units) than jejunum (0·65(0·05) units) ($P = 0·0005$). Increasing ischaemic times in the ileum resulted in decreasing nitric oxide levels (85, 32 and 13 per cent of basal level at 30, 60 and 90 min respectively); reperfusion resulted in further nitric oxide reduction (mean decrease 26 per cent). Severe (grade 3) histological damage was observed in low nitric oxide states (after 15 min of I/R in jejunum, 60 min of I/R in ileum).

Conclusion: Nitric oxide can be measured in intestinal tissues directly by EPR. The findings support a protective role for nitric oxide in I/R, and offer an explanation for the greater resistance to I/R of ileum.

Paper accepted 6 June 1999

British Journal of Surgery 1999, 86, 1427–1432

Introduction

Intestinal ischaemia occurs in a wide variety of clinical manifestations including mesenteric vascular occlusion, incarcerated hernia, intestinal volvulus and neonatal necrotizing enterocolitis[1,2]. Graft ischaemia is also inevitable during small bowel transplantation. Intestinal ischaemia adversely affects remote organs such as the lungs[3] and liver[4]. Although re-establishment of blood flow is essential to rescue ischaemic tissues, reperfusion paradoxically initiates a sequence of biochemical and cellular events that lead to further tissue damage. While the exact mechanisms involved in ischaemia–reperfusion (I/R) injury remain largely unknown, there is agreement that free radicals such as nitric oxide play an important role at the cellular and microvascular levels[5–7].

Because of the short half-life of nitric oxide free radical, its detection is difficult. Previously measurement has been done indirectly using chemiluminescence, conversion of oxyhaemoglobin to methaemoglobin or by measuring the stable metabolites of nitric oxide such as nitrite and nitrate[8]. Most studies, especially those involving systemic administration of nitric oxide inhibitors, suggest that nitric oxide and nitric oxide-releasing substances have a protective role in intestinal I/R[9–13]. Other studies, however, have depicted a harmful role for nitric oxide in I/R, as overproduction can result in systemic hypotension and local production of cytotoxic radicals[14]. These conflicting results reflect the difficulty of interpreting indirect measurements of a molecule that has many vital regulatory functions[15].

The first aim of this study was to develop a method of direct measurement in tissue which might help elucidate the real-time events involving nitric oxide during intestinal I/R. Nitric oxide has an unpaired electron that allows its detection by electron paramagnetic resonance (EPR) spectroscopy. It is highly unstable and binds strongly to materials such as iron to form a complex with a characteristic signal. Because of its binding to haemoglobin, nitric oxide can be evaluated in systemic erythrocytes[16] but for detection in tissues, a suitable preinjected electron trapper is necessary[17,18].

Previous work from this department has shown that ileum is more resistant to I/R injury than jejunum but the mechanism is unknown[19]. The second aim of this study was to evaluate nitric oxide production in ileum and jejunum during I/R and correlate the results with histological findings.

Materials and methods

Animal preparation and the nitric oxide trapping procedure

Six male Sprague–Dawley rats, weighing between 250 and 400 g were fasted overnight in individual stainless-steel cages but allowed water *ad libitum*. The animals were anaesthetized by an intraperitoneal injection of sodium pentobarbital 40 mg per kg body-weight and atropine sulphate 0·05 mg per kg body-weight. Intraperitoneal diethyldithiocarbamate (DETC) (Aldrich Chemicals, Milwaukee, Wisconsin, USA) 600 mg per kg body-weight and subcutaneous ferrous citrate complex (ferrous sulphate heptahydrate 50 mg/kg and sodium citrate 250 mg/kg) (Sigma Chemicals, St Louis, Missouri, USA) were administered 30 min before laparotomy.

Laparotomy was performed via a midline incision. In each experiment, a control sample was taken from the proximal jejunum and distal ileum at time zero. The sample consisted of an intestinal segment 2·5 cm long which was subdivided into a 2-cm segment for nitric oxide study and a 0·5-cm segment for histological analysis. Samples for nitric oxide study were immediately frozen and kept at liquid nitrogen temperature (– 196°C) for EPR analysis. Samples for histology were fixed in 10 per cent buffered formalin. Six segments of jejunum and six segments of ileum, each 5 cm long, were transected and isolated with their vascular pedicles intact (*Fig. 1*). The bowel segments were rendered ischaemic by individually occluding the terminal vascular pedicles (both arteries and veins) with soft vascular clamps. The procedure was performed meticulously by a specialist surgeon to ensure that the bowel was not damaged by preparation. At ischaemic time 15 min, half of an isolated bowel segment was removed (specimen 1). This 2·5-cm sample of ischaemic bowel was divided into a 2-cm portion for EPR study and a 0·5-cm portion for histological analysis. The vascular clamp 1 was then released. After 25 min of reperfusion, the remaining bowel (specimen 1#) was removed similarly for EPR spectroscopy and histological examination. The procedure was repeated for bowel segment pairs 2 and 2#, 3 and 3#, 4 and 4#, 5 and 5#, and 6 and 6# for intervals of ischaemia of 30, 45, 60, 75 and 90 min respectively, and reperfusion of 25 min each. Jejunal and ileal samples were harvested at the same time. Colour Doppler ultrasonography was used to confirm complete occlusion of blood flow to the bowel segments during clamping and restoration of blood supply following release of the clamps. Doppler study was also performed to confirm that blood flow to the remaining bowel was unaffected by clamping. The experiment was repeated in six rats to give a total of six sets of data for each I/R interval.

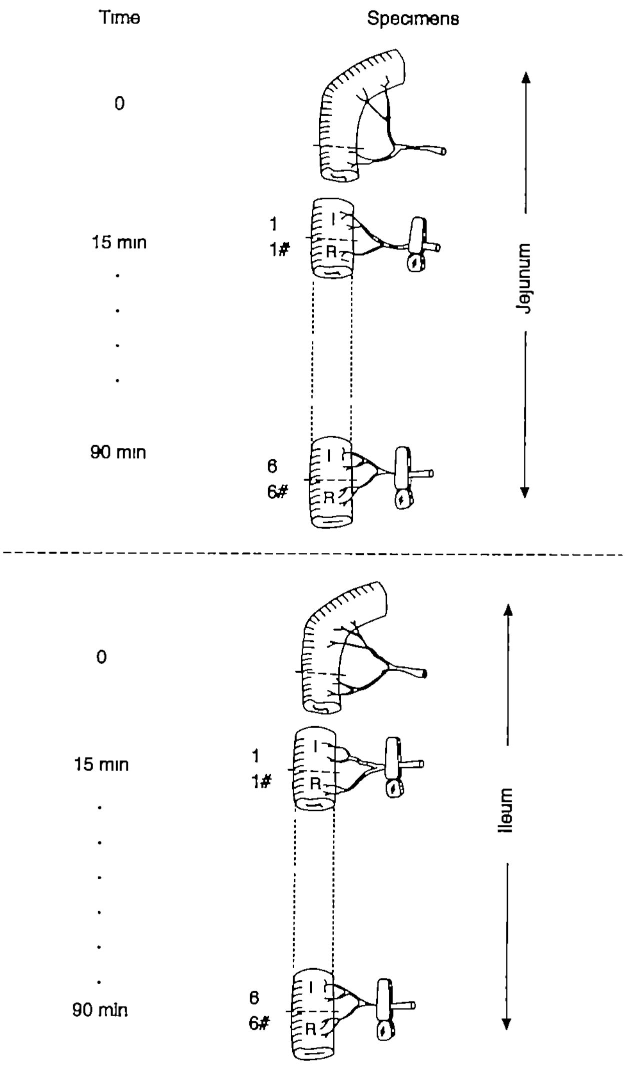

Fig. 1 Schematic drawing of the schedule of the ischaemia (I) and reperfusion (R) process for segments of jejunum and ileum. Segments 1–6 had ischaemia for 15–90 min. Segments 1#–6# had, in addition, reperfusion for 25 min before removal for electron paramagnetic resonance spectroscopy and histological studies

Stability of nitric oxide ferrous diethyldithiocarbamate complex

The stability/decay of nitric oxide ferrous diethyldithiocarbamate NOF(DETC) was studied in a second group of six rats with DETC and ferrous citrate injected 30 min before laparotomy but with no intestinal I/R. Segments of jejunum and ileum were removed at 30, 45, 60, 75, 90, 105, 120 and 135 min for EPR study.

Electron paramagnetic resonance measurement

EPR spectra were recorded using a spectrometer system (model ESP 300E; Brüker, Silberstreifen, Germany) with a liquid nitrogen cryostat so that the sample was kept at a temperature of − 196°C. EPR measurements were carried out at a microwave frequency of 9·33 GHz (X band) operated with a power of 10 mV, while the modulation frequency was 100 kHz. The magnetic field was scanned with a sweep rate of 0·48 mT/s having a time constant of 10·24 ms and a modulation amplitude of 0·32 mT. The receiver gain of the machine was 2×10^4. A quartz tube with a diameter of 4 mm was used to hold the intestinal specimen. Tissues were placed within 25 mm of the bottom of the tube. Microwave from the wave guide covered a fixed length of 20 mm for each measurement, so that each EPR signal intensity (for a certain free radical) measured the relative amount of electron spin and thus the amount of that free radical in the specimen.

A typical EPR spectrum of a rat intestinal segment with ferrous diethyldithiocarbamate F(DETC) as spin trap is shown in *Fig.* 2. The NOF(DETC) complex reveals signals at g = 2·035 and g = 2·020 with triplet hyperfine structure (HFS) at g. The signal at g = 2·00 is the third component of HFS contributed by the copper diethyldithiocarbamate complex. The signal at g = 1·94 arises from the reduced iron-sulphur proteins. The EPR signal obtained in this system is identical to that described in a study quantifying nitric oxide in the livers of mice *in vivo*[17]. The concentration of NOF(DETC) was shown to correspond directly to the height of the first peak (g = 2·047) of the standard triplet from the baseline, after normalization. This method of measuring nitric oxide was adopted in the present study and verified as follows. Saturated nitric oxide solution (2 mmol/l at 25°C and 1 atmosphere pressure) was used to calibrate the EPR system. The height of the EPR signal was found to have a linear relation with nitric oxide concentration up to at least 20 µmol/l.

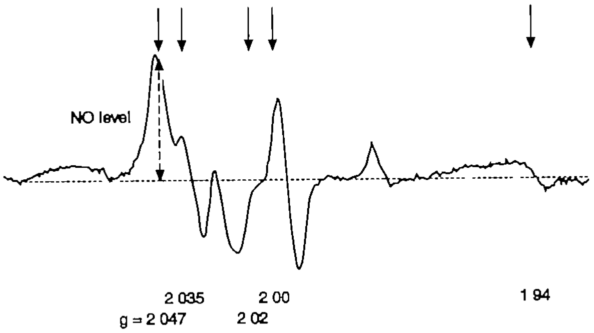

Fig. 2 A typical electron paramagnetic resonance signal in rat intestine using ferrous diethyldithiocarbamate as spin trap. The nitric oxide level was calculated from the height of the first peak (g = 2·047) of the standard triplet after normalization of the data (see text)

Histological study

The severity of I/R injury was assessed by one blinded observer (an experienced pathologist) using a classification modified from Chiu *et al.*[20]: grade 0, normal mucosa or mucosa with only mild oedema; grade 1, apical sloughing of the villi with variable congestion or oedema of the lamina propria; grade 2, epithelial damage involving at least the upper half of the villi; grade 3 (severe), epithelial damage with total or near total villous sloughing and significant involvement of the crypt epithelium.

Statistical analysis

Data were expressed as mean(s.d.) and were analysed using Kruskal–Wallis one-way analysis of variance (ANOVA). Statistical significance was reached at $P < 0.05$.

Results

Stability of NOF(DETC)

No decay of the NOF(DETC) EPR signal was observed in either ileum or jejunum in the first 75 min after laparotomy. In ileum, there was a progressive decrease in nitric oxide level from 90 min onwards: the mean nitric oxide level was 82 per cent of the basal level at 90 min ($P > 0.05$), 50 per cent at 105 min ($P < 0.05$) and 36 per cent at 120 min ($P < 0.05$). In jejunum, which had a lower basal level, no significant difference in nitric oxide level was observed at 90, 105 and 120 min.

Nitric oxide levels in ileum and jejunum

The mean(s.d.) control nitric oxide level was significantly higher in ileum (3·39(1·42) units) than jejunum (0·65(0·05) units) ($P < 0.0005$).

In ileum, during ischaemia, apart from a small increase in nitric oxide level at 15 min, increasing the duration of

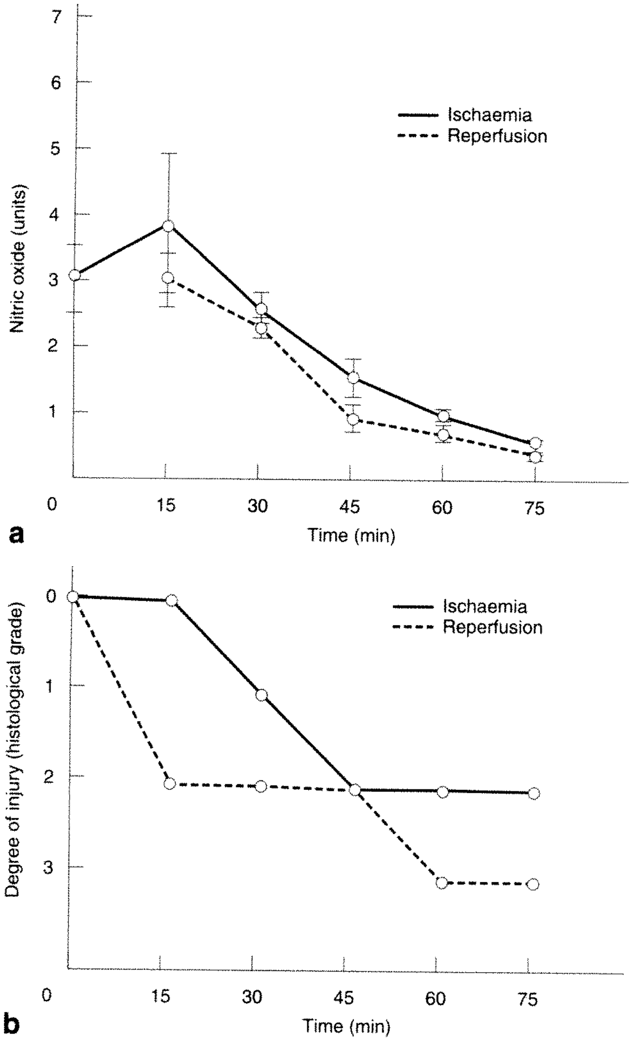

Fig. 3 **a** Nitric oxide levels and **b** degree of injury (histological grade, as defined in text) at different periods of ischaemia and 25 min of reperfusion afterwards in rat ileum. Values are mean(s.d.)

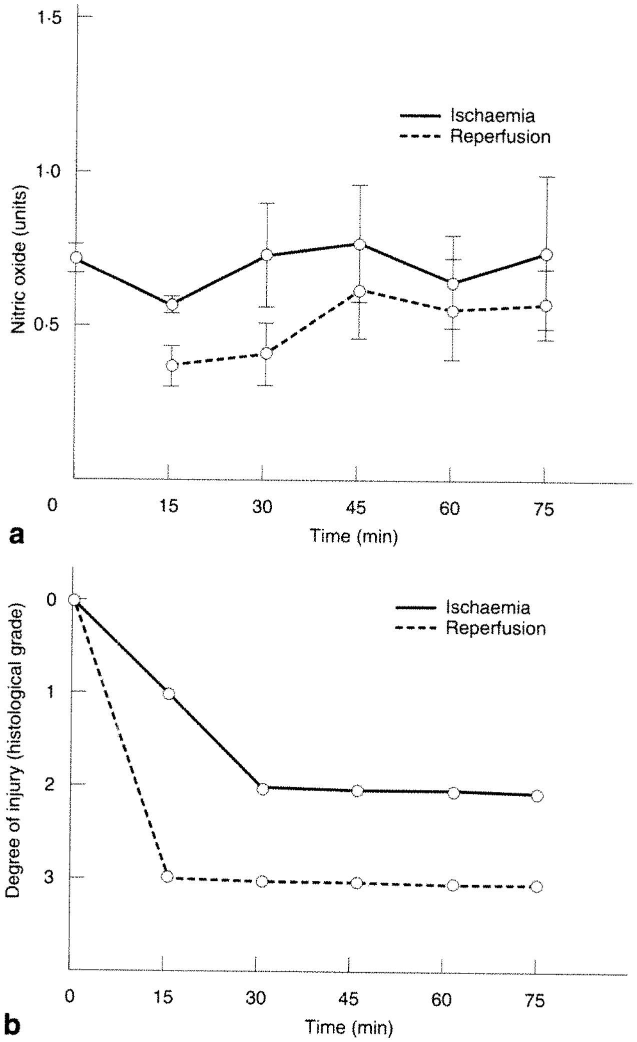

Fig. 4 **a** Nitric oxide levels and **b** degree of injury (histological grade) at different periods of ischaemia and 25 min of reperfusion afterwards in rat jejunum. Values are mean(s.d.)

ischaemia resulted in decreasing nitric oxide levels ($P < 0.05$). Reperfusion invariably resulted in a further decrease in nitric oxide levels (overall mean decrease 26 per cent) ($P < 0.05$) (*Fig. 3*).

In jejunum, the basal nitric oxide level was low and showed no further change during increasing periods of ischaemia. As in ileum, reperfusion was associated with decreased nitric oxide levels ($P < 0.05$) (*Fig. 4*).

Histologically, ileum was more resistant to I/R injury than jejunum (*Fig. 5*). Reperfusion resulted in greater tissue damage than was observed at the end of ischaemia. In ileum, increasing histological damage due to I/R correlated with decreasing nitric oxide levels as the duration of ischaemia lengthened. Grade 3 histological damage occurred in ileum after 60 min of ischaemia and subsequent reperfusion, as the mean nitric oxide level fell to 0·72 units (*Fig. 3b*). In jejunum, grade 3 damage occurred after only 15 min of ischaemia and subsequent reperfusion, corresponding to a low nitric oxide level in the basal state and a further decrease in nitric oxide level on reperfusion (*Fig. 4b*).

Discussion

The present study reports the application of EPR for direct measurement of nitric oxide production in intestinal tissues. The EPR triplet signal is unequivocal evidence of nitric oxide. Nitric oxide can be bound to haemoglobin. During

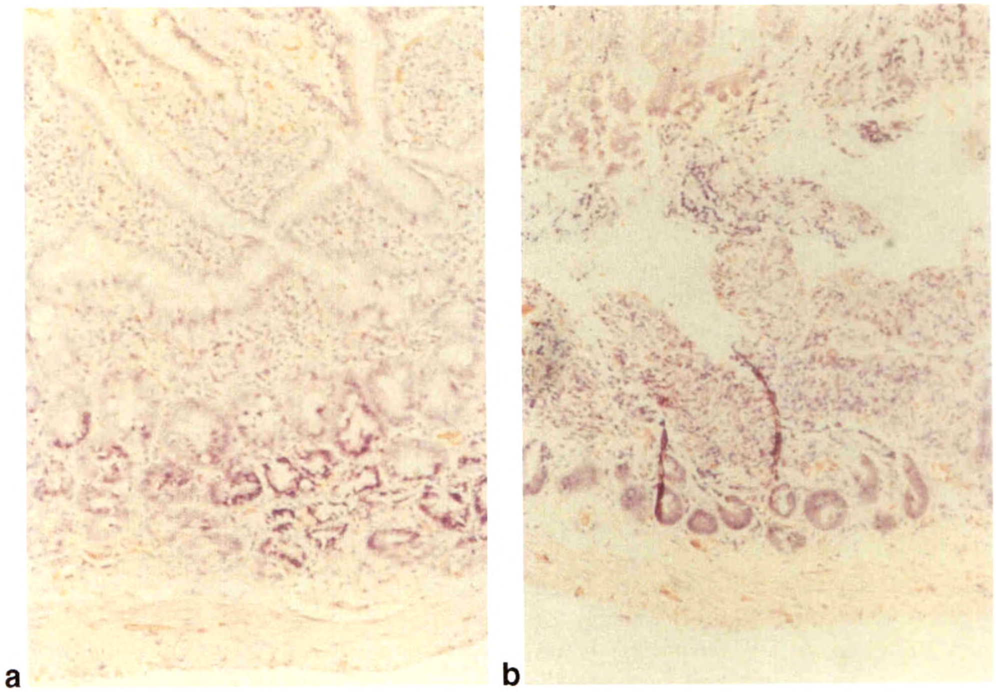

Fig. 5 Histology after 15 min of ischaemia and subsequent reperfusion.
a Ileum, in which no ischaemia–reperfusion injury can be detected.
b Jejunum with grade 3 injury; severe epithelial damage is evident with near total villous sloughing and involvement of crypt epithelium. (Haemotoxylin and eosin stain, original magnification × 100)

ischaemia, haemoglobin-bound nitric oxide may accumulate in the ischaemic intestine but the general EPR machine is not sensitive enough to detect the signals originating from haemoglobin-bound nitric oxide. To capture the presence of nitric oxide at the site of production, an electron spin trapper has to be used instead. DETC/ferrous citrate was chosen as others have successfully applied this nitric oxide trapper for study of nitric oxide unrelated to I/R in liver[17] and study of nitric oxide related to I/R in brain[18]. The spin trapper DETC/ferrous nitrate is distributed to intestinal tissues following systemic injection. The amount given in this study was sufficient to trap up to 2 μg nitric oxide per g of wet tissue, which is well in excess of the limit of endogenous nitric oxide production[17]. Hence, any increase in NOF(DETC) level detected was due only to enhanced production of nitric oxide, not to an increase in F(DETC) used to trap it.

In the present study, decay of the trapping agent in the experimented animal became significant after 75 min. Analysis of nitric oxide level by this method would therefore not have been meaningful after more than 75 min of I/R. This, fortunately, was not necessary in the rat model as the critical period of intestinal I/R injury is within 75 min. There are species differences; in pigs severe I/R injury occurs after 5 h in ileum and 1·5 h in jejunum[19]. Modification of the EPR method with the use of a different trapping agent may be necessary under these circumstances.

The present study showed an inverse relationship between intestinal I/R injury and nitric oxide free radical production. Histologically, the rat ileum appeared to be more resistant to I/R injury than jejunum, a finding that agreed with the previous porcine study from this department[19]. Interestingly, the basal nitric oxide level was higher in ileum than jejunum. Increasing the duration of ischaemia in ileum was also associated with decreasing nitric oxide levels. This inverse relationship was not observed in jejunum. This may be explained by the low basal nitric oxide level in jejunum which reached a low steady-state as soon as I/R commenced. Alternatively, the system may not have been sensitive enough to show the variations at low nitric oxide levels. This is less likely because the nitric oxide level was consistently lower on reperfusion than that observed with ischaemia alone. The deleterious effect of reperfusion was confirmed by histological upgrading of injury in both ileum and jejunum. The implication of nitric oxide in this process was strengthened by the finding of a decrease in nitric oxide level on reperfusion in both ileum and jejunum at various time points. Severe (grade 3) histological injury occurred after 15 min of I/R in jejunum and 60 min of I/R in ileum when nitric oxide levels were low.

Nitric oxide is normally synthesized from L-arginine by nitric oxide synthase which consists of constitutive and inducible isoforms. In some animal experiments, despite a reduction in constitutive nitric oxide synthase throughout I/R[21], there is rapid induction of inducible nitric oxide synthase during ischaemia, with an increase in total nitric oxide (from inducible nitric oxide synthase) during reperfusion[22]. However, inhibition of nitric oxide synthase has been shown to cause increased intestinal injury that can be prevented by exogenous L-arginine[11]. The finding of low nitric oxide production during I/R in the present study is in agreement with a protective role of nitric oxide in I/R.

Living-related segmental small bowel transplantation might become a clinical possibility and may result in a lower incidence of rejection owing to a closer human leucocyte antigen donor–recipient match than cadaveric grafting[23]. However, the best bowel segment to use has yet to be defined. A segment that can resist I/R injury would be preferred as only a limited length of bowel is available for use as an allograft. Resistance to I/R should also be an advantage in an immunosuppressed and nutritionally depleted recipient who may experience problems in the healing of severely injured allografts. The present results support the use of ileum for segmental small bowel transplantation and suggest that further studies to reduce I/R injury by pharmacological manipulation of the nitric oxide metabolic pathway are warranted.

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Original article

Improved management of infrainguinal bypass graft infection with methicillin-resistant *Staphylococcus aureus*

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Background: There is considerable debate over the management of infected infrainguinal grafts. This report describes recent experience in this field and documents the change in clinical practice needed to deal with methicillin-resistant *Staphylococcus aureus* (MRSA).
Methods: All infected infrainguinal grafts between January 1991 and July 1997 were reviewed. In the light of the findings, clinical practice was modified considerably. A further 1 year was audited prospectively up to August 1998.
Results: Twenty-six patients were treated for 27 infrainguinal graft infections (25 prosthetic, two vein). Twenty were treated by complete graft excision as the initial therapy; graft preservation was attempted in six patients. Before 1995, the infecting organisms were predominantly *Pseudomonas aeruginosa* or methicillin-sensitive staphylococci. Subsequently all 14 patients treated up to 1997 had infection with MRSA. The overall amputation rate was 17 of 26; ten amputations were in patients with MRSA. Four patients died, all with MRSA sepsis. As a result of this experience a policy of complete isolation was adopted for all patients infected with MRSA. In the 12 months since this policy was introduced, 77 infrainguinal grafts (61 vein, 16 prosthetic) have been inserted. Two grafts (3 per cent) have become infected, necessitating graft excision and amputation.
Conclusion: MRSA infection of an infrainguinal graft is a serious complication with high associated amputation and mortality rates. Isolation and barrier nursing appeared to contain the problem.

Presented in part to the annual meeting of the Vascular Surgical Society of Great Britain and Ireland, London, UK, November 1997 and published in abstract form as *Br J Surg* 1998, **85**: 564
Paper accepted 4 July 1999
British Journal of Surgery 1999, **86**, 1433–1436

Introduction

There is considerable controversy over the best treatment for patients who develop infection of an infrainguinal bypass graft. Some authors favour a policy of selective graft preservation[1–3], whereas others recommend primary excision of the infected graft with repeat grafting through clean tissue planes[4,5]. A number of different factors needs to be taken into account. The presence of active bleeding, anastomotic disruption and systemic sepsis are generally accepted indications for radical graft excision. On the other hand, infection confined to a short segment, particularly of an autogenous vein graft, may be an indication for attempted preservation. The other important factor is the virulence of the bacteria that cause graft infection[6]. In the light of an apparent increase in the incidence of infrainguinal graft infection in this institution, and a change in the causative organisms, the experience in this field over a 7-year interval was reviewed. As a result of this study it was decided to modify clinical practice considerably and the findings of a 1-year prospective audit performed since the instigation of these changes are also presented.

Patients and methods

Between January 1991 and July 1997, 26 patients were treated for infrainguinal graft infection in the St Mary's Regional Vascular Unit. There were 18 men and eight women of median age 66 (range 44–88) years. There were 17 femoropopliteal grafts (15 polytetrafluoroethylene (PTFE), one vein, one Dacron (Du Pont, Stevenage, UK)) and ten femorotibial grafts (nine PTFE, one vein). One patient suffered infection of two grafts. Eighteen patients presented with groin symptoms or signs (*Table 1*). Twenty

Table 1 Mode of presentation of infrainguinal graft infection in 26 patients

	No. of infections
Groin	
Sinus	9
False aneurysm or bleeding	8
Lump	1
Other wound sinus or exposed graft	6
Pyrexia or rigors	6
Septic emboli	2

Some patients had more than one infection

patients were treated by primary graft excision. In four, a new autogenous vein graft was placed through sterile tissue planes to achieve limb salvage. Six patients were initially treated with attempted graft preservation. This involved thorough wound debridement, sartorius flap coverage of exposed graft (two patients) and/or closed irrigation with gentamicin. One patient in this group had an infected midthigh portion of graft excised and replaced with a segment of autogenous vein tunnelled through uncontaminated tissue planes. All patients received target parenteral antibiotics. After 1995 vancomycin was commenced routinely on admission, usually in combination with other broad-spectrum antibiotics.

Results

The median interval between graft placement and presentation with signs of infection was 3 (range 1–36) months. In patients with methicillin-resistant *Staphylococcus aureus* (MRSA) the median was 2 (range 1–12) months. Twenty of the 26 patients presented within 6 months. Over the years of this study the organisms isolated changed significantly (*Table 2*). Before 1995 the principal pathogens were methicillin-sensitive *Staphylococcus aureus* and *Pseudomonas aeruginosa*. From 1995 onwards, although *Pseudomonas* was also cultured in two patients, the main infecting organism in all 14 patients was MRSA. A number of different phage types was identified (especially types 15 and 16), but the severity of the clinical infection was not related to phage type. Twenty-one of the 26 patients had the original graft placed at St Mary's Hospital, and five were referred from other hospitals. Three of the 15 patients with MRSA infection came from other institutions. The annual incidence of infrainguinal graft infection in 1991 was 3 per cent. This rose to 11 per cent in the first 7 months of 1997 (*Fig. 1a*). This difference was not statistically significant. For PTFE grafts (*Fig. 1b*), the infection rate was two of 34 in 1991, compared with seven of 16 for the first 7 months of 1997 ($P < 0{\cdot}01$, χ^2 test, Yates 0·998).

Of the 20 patients treated primarily with graft excision, 15 required leg amputation. Limb salvage was achieved in five of this group, in four by means of a new vein bypass graft.

Only one of the six patients treated initially by attempted graft preservation managed to retain the graft (midgraft excision and vein graft interposition). The remaining five patients required complete graft excision at subsequent operation because of ongoing or recurrent sepsis. Limb salvage was achieved by complete graft replacement in three of these patients, but major limb amputation was required in two.

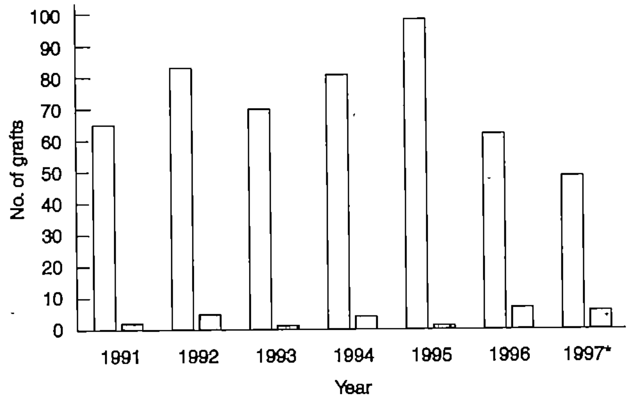
Of the 15 patients with infrainguinal graft infection due to MRSA, ten required amputation; four died from MRSA sepsis. Limb salvage was achieved in five patients with MRSA (in four by means of a new vein graft). Seven of the 11 patients with non-MRSA infection had amputation, and limb salvage was achieved in four (three replacement vein grafts, one graft revision).

Overall, 17 of 26 patients required amputation. Four patients died, all from MRSA sepsis, giving a 30-day mortality rate of four of 26. The amputation rate was similar

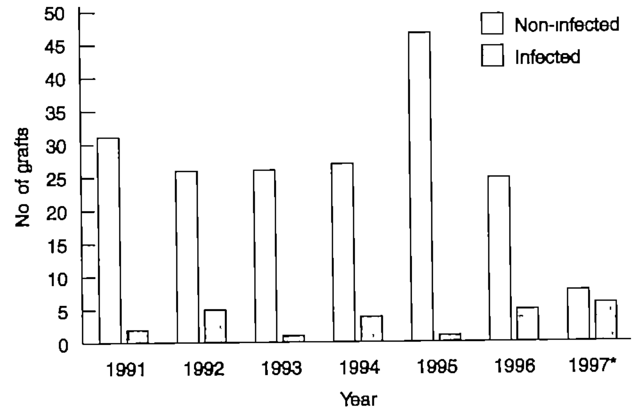
Table 2 Bacteriology of infrainguinal graft infection in 26 patients

	MRSA	MSSA	*Pseudomonas aeruginosa*	*Enterococcus* species	Coagulase-negative *Staphylococcus aureus*	No growth
1991	0	1	0	0	0	1
1992	1	2	1	0	0	1
1993	0	1	0	0	0	1
1994	0	0	2	1	1	0
1995	1	0	0	0	0	0
1996	7	0	1	0	0	0
1997	6	0	1	0	0	0

No organisms were cultured in two patients; two organisms were isolated in four patients (see text). MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*



a All grafts



b Polytetrafluoroethylene grafts

Fig. 1 Annual incidence of graft infection. *Up to August 1997

for MRSA (ten of 15) and non-MRSA (seven of 11) infections, but all the deaths were in patients with MRSA.

As a result of this experience (an apparent increase of infrainguinal graft infection together with a change of infecting organism to MRSA) it was decided to isolate all patients known to be colonized or infected with MRSA. A four-bed side ward was converted for these patients. This room had its own separate washing and toilet facilities. Nursing staff were allocated to the isolation bay only and the number of personnel entering it was kept to an absolute minimum. Ward practice was changed so that wound inspections were conducted by appointment, using strict barrier techniques. The MRSA status of all transfer patients was established at the referring hospital. An absolute limit on the number of MRSA-infected inpatients was set at six (the isolation unit and two separate side rooms).

In the 12 months between August 1997 and August 1998, 77 infrainguinal bypass grafts were inserted at this institution (61 vein, 16 PTFE). During this time two patients required complete graft excision and limb amputation because of MRSA graft infection, which became apparent 2 and 3 months after graft placement. Two further patients had MRSA infection of calf wounds in relation to distal PTFE grafts. At operation it was clear that the (patent) grafts were incorporated and not overtly infected, but they were excised nevertheless and amputation was necessary. Four other patients colonized with MRSA underwent vein bypass without infective complication. The graft infection rate for this 12-month interval was 3 per cent (two of 77). Thus, in spite of MRSA being the predominant infecting organism, since instituting the changes in clinical practice the graft infection rate (3 per cent) and infection-related amputation rate (5 per cent; four of 77) appear to have reduced to a level similar to that in the era before MRSA infection appeared.

Discussion

This experience with the management of infrainguinal graft infection has raised a number of controversial issues. Infection is much more common in distal PTFE grafts inserted for critical ischaemia. The case for attempting initial graft preservation has been made forcefully by several authors[1,3,7]. Whilst graft conservation is a desirable concept, few patients in the present study were successfully managed this way. This is similar to experience with aortoiliac graft infection at this hospital[8]. The majority of patients in the present study developed septic anastomotic disruption in the form of infected false aneurysm or active haemorrhage, often in association with systemic sepsis or septic distal emboli. When graft conservation was attempted in the present series all but one patient ultimately required graft excision, often because of recurrent sepsis. In a series of 27 infected infrapopliteal grafts Calligaro *et al.*[2] attempted graft preservation in 12. Five suffered further infection and two died, questioning the advisability of such an approach. Cherry *et al.*[3] had an unfavourable experience with PTFE graft sepsis and recommended primary excision for infection.

It is commonly agreed that absolute indications for complete graft excision as the primary surgical management of an infected infrainguinal graft are: systemic sepsis, anastomotic disruption and graft occlusion[1,6]. In the light of the data from this paper it is suggested that MRSA infection should be added to this list.

There was a higher amputation rate (17 of 26 patients) in this study than that reported by other authors (usually between 20 and 30 per cent)[2,3,9]. This can be attributed to the number of patients with critical leg ischaemia in the study. The associated high morbidity of MRSA graft infection also contributed to the high amputation rate.

MRSA infection is becoming an increasing problem in hospital practice. In vascular surgery the majority of infrainguinal grafts are inserted fairly urgently. Patients have often had recent contact with hospital before their operation, or else are transferred from another specialty where MRSA colonization is a significant problem, for example geriatric and renal medicine[10]. Graft infection with MRSA is an early phenomenon and the mode of infection is presumably direct seeding from colonized skin at the time of operation[9]. There are a number of strains of MRSA, perceived to have varying virulence. Most hospitals seem to have indigenous strains but other phage types are introduced when patients are transferred[11]. The severity of infection in individual patients does not seem to be related to any particular MRSA phage type, but the general status of many vascular patients (concomitant diabetes, ischaemic tissue, cardiac disease, etc.) makes them vulnerable to infection from apparently 'innocuous' strains of MRSA.

If a patient is transferred from another hospital with an acute complication of graft infection (haemorrhage or false aneurysm), it should now be assumed that MRSA is the infecting organism until proven otherwise by bacteriological culture. At St Mary's the surgical approach is to remove all prosthetic graft material and to revascularize the affected limb with autogenous vein graft routed through clean tissue planes. Subtotal excision, leaving a cuff of graft at the anastomosis, is appealing but may result in late sinus formation. It may be necessary to close the femoral artery with an autogenous patch (vein or endarterectomized superficial femoral artery) to maintain profunda flow. After debridement the repair may be covered with a sartorius flap and the wound closed, allowing for irrigation with gentamicin or vancomycin. If revascularization is not an option, amputation can be done either at the same procedure or within 24–48 h.

With regard to antibiotic policy, Calligaro and Veith[7] have recommended that, irrespective of Gram stain results, all patients should be treated with vancomycin and ceftazidime from the time of presentation with infrainguinal graft infection. This policy is supported at St Mary's, as well as agreeing with the recommendations of Fletcher *et al.*[12] that anti-MRSA antibiotic prophylaxis be used routinely for all revisional vascular surgery.

In conclusion, MRSA appears to be an increasing cause of infrainguinal graft infection. The best treatment is complete graft excision with repeat bypass using autogenous vein tunnelled through sterile tissue planes. Unfortunately, most of the MRSA infections occurred in patients in whom PTFE had been inserted because of a lack of suitable vein for bypass. If vein is not available, graft excision should be accompanied by amputation in order to avoid ongoing MRSA sepsis, which is associated with a high mortality rate. Prosthetic graft preservation should not be attempted. The use of autogenous vein for infrainguinal bypass greatly reduces the likelihood of MRSA graft sepsis. This may mean using multiple segments of spliced vein, or even vein of suboptimal quality, rather than resorting to prosthetic graft material.

Based on a 1-year prospective audit, the isolation of infected patients, together with strict Listerian ward practice, appears to have contained the problem of MRSA infection in this unit.

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Original article

Venous ulcer healing by four-layer compression bandaging is not influenced by the pattern of venous incompetence

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Background: Previous studies have related deep venous incompetence to reduced venous ulcer healing rates. The aim of this study was to determine the relationship between the pattern of venous incompetence and ulcer healing.

Methods: A total of 198 legs with venous ulceration were investigated with colour venous duplex imaging to determine the presence and site of venous incompetence. All were treated initially with the four-layer bandage technique.

Results: At 6 months, 74 per cent of the venous ulcers had healed using the four-layer bandage technique. There was no significant correlation between the pattern of incompetence and the healing rate of the ulcer. Previous deep vein thrombosis (DVT), increased size of the ulcer and previous episodes of ulceration were associated with a poor healing rate.

Conclusion: The four-layer bandage technique achieved an ulcer healing rate of 74 per cent after 6 months, irrespective of the pattern of venous incompetence. Patients with a large ulcer, previous DVT or previous episodes of ulceration had delayed healing, supporting the previous literature.

Paper accepted 13 July 1999

British Journal of Surgery 1999, 86, 1437–1440

Introduction

Venous ulcer treatment costs the National Health Service £400–600 million per year[1]. Some 1–2 per cent[2–4] of the population are affected with a venous ulcer at some stage. Venous hypertension is recognized as the principal underlying cause due to either venous[5,6] or deep venous[7] obstruction.

The Edinburgh group found that the presence of reflux in the popliteal vein was associated with reduced healing of venous ulcers[8]. It was postulated that the popliteal vein acts as the 'gatekeeper' for the calf muscle pump. Other authors found that popliteal reflux was the most important factor in determining the ambulatory pressure in a post-thrombotic leg, as assessed by air plethysmography[9]. Several studies have highlighted the importance of the popliteal vein in the pathogenesis of venous ulceration[10–14].

The aim of this study was to evaluate patients with a venous ulcer using colour duplex imaging and to determine whether duplex findings correlated with ulcer healing rates.

Patients and methods

During a 16-month interval, 202 consecutive patients (258 legs) were assessed in a one-stop specialist leg ulcer clinic[15]. The majority were referred directly by district nurses All had ankle : brachial pressure index (ABPI) measurement performed initially, followed by venous duplex imaging by an experienced vascular technologist. Venous incompetence was defined as reflux for 1 s or more following distal augmentation[16]. The veins assessed included the long and short saphenous veins, the deep veins and the perforating veins. Patients had wound swabs and acetate mapping of the ulcer. After taking history and examination, all patients with an ABPI above 0·8 were treated initially with four-layer compression bandaging. Ulcers with an arterial component (ABPI less than 0·8) also had arterial duplex imaging. A venous ulcer was defined as a leg ulcer showing clinical evidence of venous disease (pigmentation, eczema, lipodermatosclerosis or varicose veins) and an ABPI of more than 0·8, in the absence of other aetiological factors. Some patients had ulcers diagnosed as resulting from alternative aetiologies, including arterial disease (ABPI less than 0·8) ($n = 29$), diabetes ($n = 15$), rheumatoid arthritis ($n = 3$), carcinoma (basal cell, $n = 1$; squamous cell, $n = 1$), vasculitis ($n = 1$) and trauma ($n = 11$). The total number of legs with a venous ulcer was 198 (27 per cent bilateral, 144 patients). The male : female ratio was 1 : 2·1 and median age was 76 (range 40–93) years.

Patients were seen in a leg ulcer clinic run by a district nurse at least once a week, depending on the severity of the ulcer following the initial assessment. On each occasion the four-layer bandaging was changed. All nurses had attended a standard course in the treatment of leg ulceration. In addition, the patients were seen in a hospital outpatient clinic every 8–10 weeks until the ulcer had healed, or more frequently if the ulcer was deteriorating. At each visit an acetate tracing was performed. Healing was defined as complete re-epithelialization. If the ulcer did not heal with four-layer bandaging in 6 months, the patient was considered for venous surgery, if fit and willing. If a patient had bilateral ulceration, one leg was chosen at random for the analysis.

Results

The median number of previous episodes of ulceration was 2 (range 0–7). The median size of the index ulcer was 7·5 (mean 14·2, range 1–245) cm^2. Some 74 per cent were medial, 7 per cent were lateral and 2 per cent were circumferential; 26 per cent of legs had more than one ulcer. The median duration of the ulcer before treatment was 8 (mean 13, range 1–148) months. Fourteen per cent of patients reported a previous deep vein thrombosis (DVT), 11 per cent had previous varicose vein surgery and 2 per cent skin grafting.

After 26 weeks of treatment, 107 (74 per cent) of 144 legs with venous ulcers were healed by four-layer bandaging. The distribution of venous incompetence on duplex imaging is shown in *Table 1*. There was no significant difference between the pattern of venous incompetence and the healing rate of the ulcers ($P = 0{\cdot}14$, Fisher's exact test).

A number of factors that may be related to ulcer healing were examined. The ulcer healing rate was significantly related to initial ulcer size. This was calculated using quartiles: smaller than 6 cm^2 (91 per cent healed), 6–7 cm^2 (70 per cent healed), 8–10 cm^2 (79 per cent healed), larger than 10 cm^2 (55 per cent healed) ($P = 0{\cdot}001$, χ^2 test). There was no relationship between healing and duration of ulceration using quartiles: less than 5 months (77 per cent healed), 5–8 months (69 per cent healed), 9–14 months (72 per cent healed), more than 14 months (78 per cent healed). Patients with previous episodes of ulceration were significantly less likely to heal than those without: no episodes (84 per cent healed), one or two episodes (82 per cent healed), three or four episodes (65 per cent healed), more than four episodes (53 per cent healed) ($P = 0{\cdot}052$, χ^2 test). In patients with a previous DVT, the ulcer was less likely to heal (61 *versus* 76 per cent); however, this did not reach statistical significance ($P = 0{\cdot}11$, χ^2 test).

Logistic regression was used to see whether there was any association between the pattern of incompetence and healing after adjusting for ulcer size, duration, previous episodes of ulceration and previous DVT. These were factors shown by other authors to be associated with a poor healing rate. After adjusting for these variables, there was still no evidence that the pattern of venous incompetence was independently associated with healing; this was assessed using a likelihood ratio test ($P = 0{\cdot}51$).

Table 1 Pattern of venous incompetence on duplex imaging and healing rates in 144 legs

Pattern of incompetence	No. of legs	No. healed
No reflux	15	9 (60)
Superficial only	21	14 (67)
Perforator only	4	2 (50)
Deep only	8	6 (75)
Superficial and perforator	43	33 (77)
Superficial and deep	7	4 (57)
Perforator and deep	5	3 (60)
Superficial, perforator and deep	41	36 (88)
Total	144	107 (74)

Values in parentheses are percentages. There was no evidence of an association between pattern of incompetence and healing ($P = 0{\cdot}14$, Fisher's exact test)

Table 2 Relationship between segment of venous incompetence and ulcer healing rate

	Proportion healed*		
Venous segment	No reflux	Reflux	P†
Saphenofemoral junction	37 of 48	41 of 53	0·97
Long saphenous vein (above knee)	37 of 48	53 of 70	0·86
Long saphenous vein (below knee)	33 of 42	54 of 72	0·67
Saphenopopliteal junction	75 of 99	13 of 14	0·15
Short saphenous vein	49 of 66	36 of 46	0·63
Deep thigh veins	56 of 72	30 of 38	0·89
Popliteal vein	36 of 61	34 of 46	0·11
Deep calf veins	56 of 75	30 of 38	0·61
Perforator veins (above knee)	59 of 86	15 of 21	0·80
Perforator veins (below knee)	27 of 40	58 of 71	0·09

*Number of ulcers healed related to reflux in each venous segment. †χ^2 test

The power of the analysis was increased by dividing the patients into two groups: those with deep venous incompetence ($n=61$) and those with normal deep veins ($n=83$). Both the univariate (unadjusted) analysis and adjusted analysis were repeated. Ulcers healed in 48 (79 per cent) of 61 patients with deep vein incompetence compared with 59 (71 per cent) of 83 with normal deep veins. There was no evidence of an association between the pattern of incompetence (after grouping) and healing (test statistic 2·01, 1 d.f., $P=0{\cdot}16$; Pearson χ^2 test) Logistic regression using a likelihood ratio test in the adjusted analysis indicated that there was still no evidence that the pattern of incompetence after grouping was independently associated with healing ($P=0{\cdot}47$). This took into account the other factors mentioned above known to be associated with adverse healing. The relationship between healing rate and incompetence at each venous segment is shown in *Table 2*. There was no evidence of an association for any of the segments ($P>0{\cdot}05$).

Discussion

This study has shown satisfactory healing rates for venous ulcers treated with four-layer compression bandaging. The distribution of venous incompetence in the legs treated is in agreement with other similar studies[17,18]. The ulcers with no venous reflux on duplex imaging were in one of the worst healing groups (although this was not significant and the number of patients in this group was small). Randomized controlled clinical trials have not yet been performed to determine the role of superficial venous surgery plus compression bandaging in patients with a venous ulcer. There is some evidence that surgery may improve ulcer healing and recurrence rates[19,20].

Healing rates were poorer (but not significantly so) in post-thrombotic legs, although the number in this group was small ($n=20$). The trend in this study supports the results of others suggesting that previous DVT is an adverse prognostic factor in the healing of venous ulcers[21]. Similarly, ulcers in patients with previous episodes of ulceration were less likely to heal[22]. Size of ulcer at presentation was significantly correlated to healing rate ($P=0{\cdot}001$), as demonstrated by others[23]. There was no relationship between duration of ulceration and healing rate.

Venous ulcers in the present study took longer to heal than those in the original published series of patients treated with four-layer bandaging (6 months to achieve a healing rate of 74 per cent compared with the original healing rate of 72 per cent after 3 months). The overall healing rate was comparable[20]. It appears that patients who are being referred have ulcers that are more difficult to heal. The district nurses have increasing confidence in managing simple leg ulcers; only patients with stubborn ulcers are referred.

This study failed to confirm the results from Edinburgh possibly because of important differences in the interventions. All patients in the present study were treated with four-layer compression bandaging. In the Edinburgh study, as part of another trial, patients were randomized to elastic single-layer or multilayer bandaging. They were also randomized to different types of dressing and therapy with oxpentifylline. While there was no significant effect of these interventions on healing, the lack of uniformity of treatments may have altered the outcome. In addition, the Edinburgh study did not appear to control for other factors thought to affect the healing of venous ulcers, such as size, previous DVT and previous episodes of ulceration.

The present study failed to show an effect of the presence of popliteal vein reflux on healing of venous ulcers treated by four-layer bandaging. There is evidence in patients with a venous ulcer treated by superficial and perforator vein surgery that the presence of primary deep vein incompetence does not affect healing[21].

With respect to size of ulcer, previous DVT and previous episodes of ulceration, there were differences that supported the previous literature to suggest that these are adverse prognostic factors in the healing of venous ulcers.

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Original article

Influence of systemic factors on pre-existing intimal hyperplasia and their effect on the outcome of infrainguinal arterial reconstruction with vein

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Background: The association between raised levels of homocysteine, fibrinogen and lipoprotein (a), and the presence of pre-existing intimal hyperplasia (IH) in vein has not been assessed. The positive association between such hyperplasia and graft failure following infrainguinal arterial reconstruction, and between lipoprotein (a) and graft failure, is disputed. The influence of homocysteine on outcome has not been investigated prospectively.

Methods: Fifty-seven patients (63 grafts) undergoing infrainguinal arterial reconstruction with saphenous vein were studied. Homocysteine, fibrinogen and lipoprotein (a) levels were measured, and a vein biopsy was taken at operation. Patients underwent graft surveillance and outcome at 12 months was determined.

Results: Fifty-seven per cent of patients had hyperhomocysteinaemia. Patients with pre-existing IH had significantly higher homocysteine levels. There was no association between homocysteine and outcome, or between fibrinogen and pre-existing IH or outcome. Lipoprotein (a) levels were significantly lower in patients with pre-existing disease, and were lower, but not significantly, in those whose grafts failed. The correlation between pre-existing IH and vein graft failure was highly significant.

Conclusion: Hyperhomocysteinaemia is associated with peripheral vascular disease and the development of pre-existing IH in vein, which itself is associated with vein graft failure.

Presented to the Surgical Research Society, in Dublin, UK, July 1998
Paper accepted 20 June 1999
British Journal of Surgery 1999, 86, 1441–1447

Introduction

Despite the increased use of infrainguinal arterial reconstruction with vein for critical ischaemia, there is little evidence of a fall in the incidence of major amputation through the 1990s[1,2], even with the advent of duplex-based graft surveillance programmes[3]. The Second European Consensus Document on critical ischaemia[4] suggested that patency rates for infrapopliteal grafts should be around 70 per cent at 1 year; nevertheless some recent series have recorded graft failure rates approaching 40 per cent[5,6]. The socioeconomic consequences of graft failure are severe, both to the individual and to purchasers of health care. The identification, and correction or avoidance, of factors associated with vein graft failure could have an impact on graft patency rates. Furthermore, the identification of factors in an individual patient may define patients at high risk of graft failure who might benefit from intensive vein graft surveillance.

The majority of grafts fail as a result of the development of neointimal hyperplasia[7]. Two approaches have been taken to identify factors associated with graft stenosis: an analysis of the influence of the 'quality' of vein used as a bypass and the identification of haematological parameters that might predispose to stenosis.

LoGerfo *et al.*[8] and Szilagyi *et al.*[9] introduced the concept of vein quality and suggested that this might influence outcome. Since then a number of investigators have detailed the occurrence of pre-existing intimal hyperplasia (IH) in vein[10], and found the presence of pre-existing disease to correlate with subsequent vein graft stenosis[11]. More recently, however, this relationship has been disputed[12].

Raised levels of plasma fibrinogen, plasma homocysteine and serum lipoprotein (a) have all been identified as risk factors for atherosclerotic disease[13–18]. A number of series have reported an association between hyperfibrinogenaemia and vein graft stenosis after arterial reconstruction[19–21]. The data implicating raised levels of lipoprotein (a) in graft failure are contradictory[21–23].

This study sought to reaffirm the association between pre-existing intimal disease and subsequent vein graft failure, and between a raised plasma fibrinogen level and graft failure. The association between lipoprotein (a) and homocysteine and vein graft failure was also investigated, and the influence of lipoprotein (a), fibrinogen and homocysteine on the development of pre-existing IH in vein was assessed.

Patients and methods

Patients undergoing infrainguinal arterial reconstruction using vein over 21 months were recruited to the study. Ethics committee approval and informed consent were obtained. On the day before surgery, venesection was performed for the estimation of levels of plasma homocysteine, plasma fibrinogen, serum lipoprotein (a) and plasma cotinine (as an indicator of current smoking status). At operation, a biopsy of long saphenous vein was taken from the segment of vein immediately distal to the most distal part of the vein graft. This was placed immediately into formal saline. After operation, all patients were entered into a duplex graft surveillance programme with assessments at 6 weeks and 3, 6, 9 and 12 months. Peak systolic velocity measurements were used to detect vein graft stenoses and graft 'failure' was deemed to have occurred where a graft had occluded or where a stenosis in excess of 50 per cent was detected. Grafts that thrombosed within 30 days of surgery were excluded, as these were likely to be technical failures.

Vein biopsy specimens

Saphenous vein specimens were embedded in paraffin; 1·5-μm sections were cut, mounted and stained with haematoxylin and eosin and elastin Van Gieson. The sections were examined by an independent histopathologist with extensive experience in the semiquantitative assessment of pre-existing changes in vein. For each specimen two scores were assigned. The first was a single semiquantitative score of pre-existing IH: 0, no IH; I, mild IH; II, moderate IH; and III, severe IH. In many instances saphenous vein exhibited pre-existing muscular hypertrophy and a second score was used to take this into account. This was a previously validated modification of the scoring system described by Milroy *et al.*[24] and is shown in *Table 1*.

Table 1 Histological grading system for scoring vein biopsies

Grade	Definition
0	Normal vein; no pre-existing fibroelastic IH; no pre-existing muscle hypertrophy
1	Mild focal pre-existing IH involving less than 50 per cent of the luminal surface or grade 0 IH plus muscle hypertrophy
2	Moderate diffuse pre-existing IH in excess of 50 per cent of the luminal surface or grade I IH plus muscle hypertrophy
3	Extensive diffuse pre-existing IH affecting more than 50 per cent of luminal surface or grade II IH plus muscle hypertrophy

IH, intimal hyperplasia

Statistical analysis

All results were expressed as mean(s.e.m.). Statistical analysis was performed using the Mann–Whitney test unless otherwise stated.

Results

Fifty-seven patients (63 grafts) were recruited, including 18 women and 39 men of median age 76 (range 34–89) years. None of the six patients who had bilateral reconstructions underwent both operations during the same admission. Thirty-four bypasses (54 per cent) were for chronic leg ischaemia, seven (11 per cent) for acute ischaemia, six (10 per cent) for intermittent claudication, five (8 per cent) for elective bypass of a popliteal aneurysm and 11 (17 per cent) were repeat grafts. Eight patients were lost to follow-up, five grafts failed within 30 days and three patients died after operation, leaving 47 grafts available for follow-up at 12 months. Vein specimens were obtained from 54 grafts. A total of 56 homocysteine samples, and 54 fibrinogen and lipoprotein (a) samples, was available for analysis.

Of the 47 grafts available for follow-up, 24 'failed' at a median of 6 (range 2–12) months after operation. Of the 24 'failures', 19 were deemed to have failed on grounds of developing a stenosis; all but three of these had stenoses of greater than 70 per cent on peak velocity criteria. Seventeen of the 19 underwent further intervention either by balloon or vein patch angioplasty, although one patient had an interposition graft. Of the five patients whose grafts occluded, only one underwent graft revision.

Relationship between pre-existing intimal hyperplasia in vein and haematological parameters.

Fig. 1 illustrates the relationship between the presence of pre-existing IH in vein used for bypass and plasma levels of fibrinogen, homocysteine and serum lipoprotein (a).

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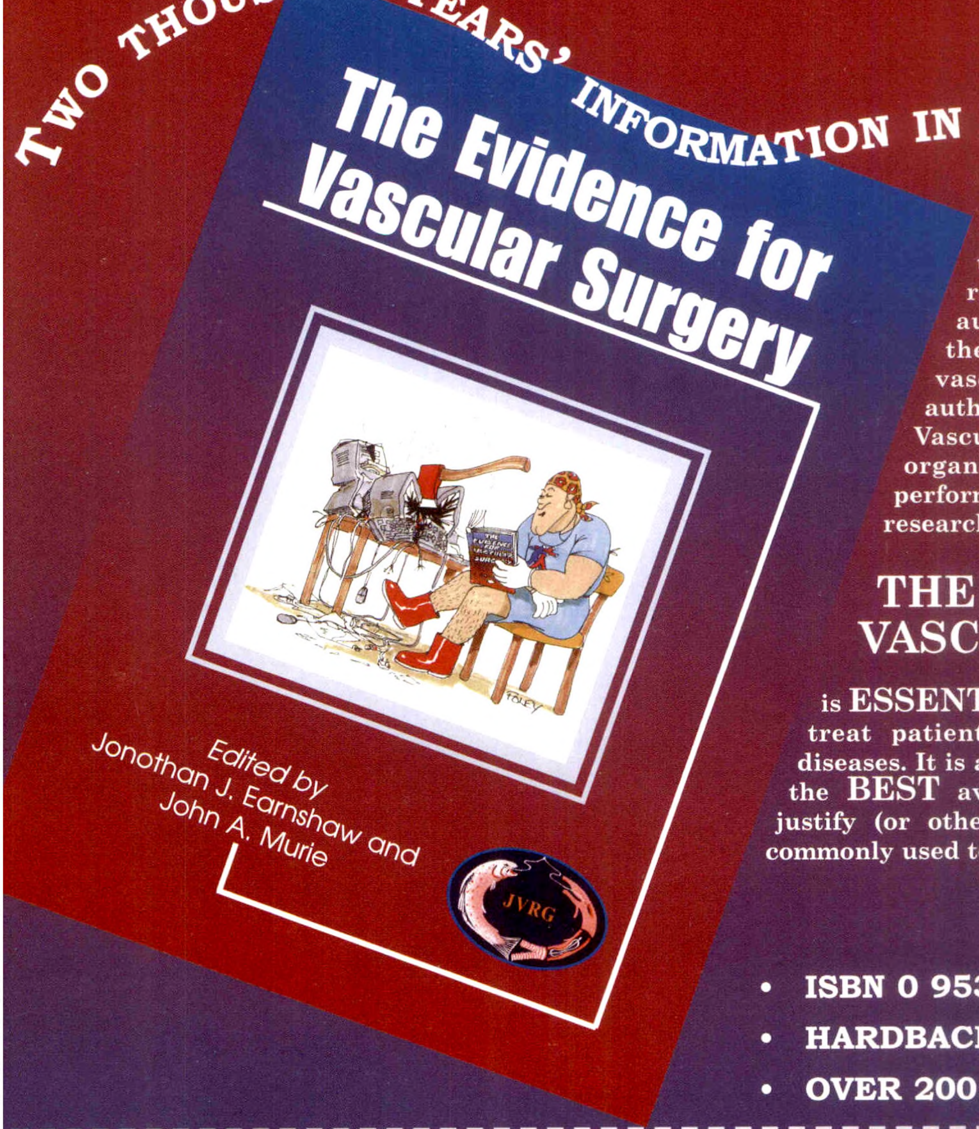

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The 95th centile for the distribution of plasma homocysteine in the normal population as determined by the authors' reference laboratory is 12·2 µmol/l for women and 15·5 µmol/l for men. Values above this were considered abnormal. Thirty-two (57 per cent) of 56 patients had a homocysteine level above this; the mean plasma homocysteine concentration for all patients was 16·9(1·2) µmol/l. Notably, 14 of 18 women who underwent bypass had homocysteinaemia and all 18 women had pre-existing IH in biopsied saphenous vein. The mean plasma homocysteine level was significantly lower in patients whose vein had no pre-existing IH (11·4(1·4) *versus* 17·9(1·5) µmol/l; *n* = 50, *P* = 0·007). There was, however, no association between hyperhomocysteinaemia and the grade of pre-existing IH (*P* = 0·23, analysis of variance).

The mean plasma fibrinogen level (*n* = 54) for all patients was 3·8(0·3) g/l which was below the reference 95th centile value of 4·8 g/l. The mean plasma fibrinogen level was higher in patients without pre-existing IH but not significantly so (4·2(0·4) *versus* 3·8(0·3) g/l; *n* = 47, *P* = 0·22).

The mean plasma lipoprotein (a) concentration for all patients (*n* = 54) was 281·2(32·8) mg/l which was just below the 95th centile reference value of 300 mg/l. Patients with no pre-existing IH had a significantly higher mean plasma lipoprotein (a) level (419·4(77·0) *versus* 217·9(35·5) mg/l; *n* = 50, *P* = 0·012) (*Fig. 1*).

Outcome analysis

There was no association between outcome and age, sex, smoking status, presence of diabetes or level of reconstruction (*Table 2*).

Fig. 2 shows the relationship between outcome and each of the haematological parameters assessed. Homocysteine levels were higher, but not significantly, in patients who went on to develop graft stenosis or occlusion (17·3(2·5) *versus* 15·9(1·7) µmol/l; *n* = 44, *P* = 0·99). Mean serum lipoprotein (a) was lower in those with a 'failed' graft, but without significance (246·0(46·4) *versus* 338·0(58·1) mg/l; *n* = 46, *P* = 0·32). Fibrinogen levels were higher in the

Table 2 Factors not related to outcome following infrainguinal reconstruction

	Patent grafts	Stenosed grafts	*P*
Median (range) age (years)	77 (49–87)	76 (34–89)	0·57*
Male sex	15 of 23	16 of 24	0·40†
Current smoker	11 of 22	10 of 22	0·38†
Diabetic	3 of 22	9 of 24	0·08†
Reconstruction to an infrapopliteal vessel	5 of 23	6 of 24	0·36†

*Mann–Whitney test; †χ^2 with Yates' correction

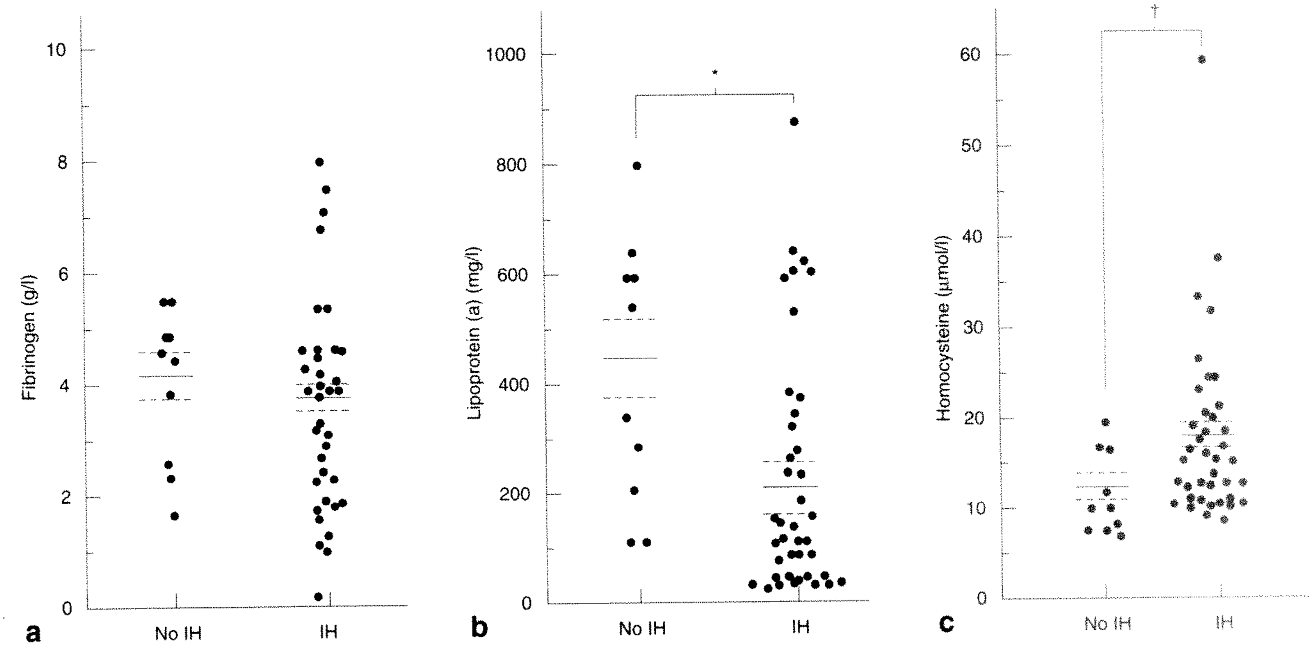

Fig. 1 Association between **a** plasma fibrinogen, **b** serum lipoprotein (a) and **c** plasma homocysteine levels, and the presence of pre-existing intimal hyperplasia (IH). Solid lines represent the mean and broken lines the s.e.m. *$P = 0.12$, †$P = 0.007$ (Mann–Whitney test)

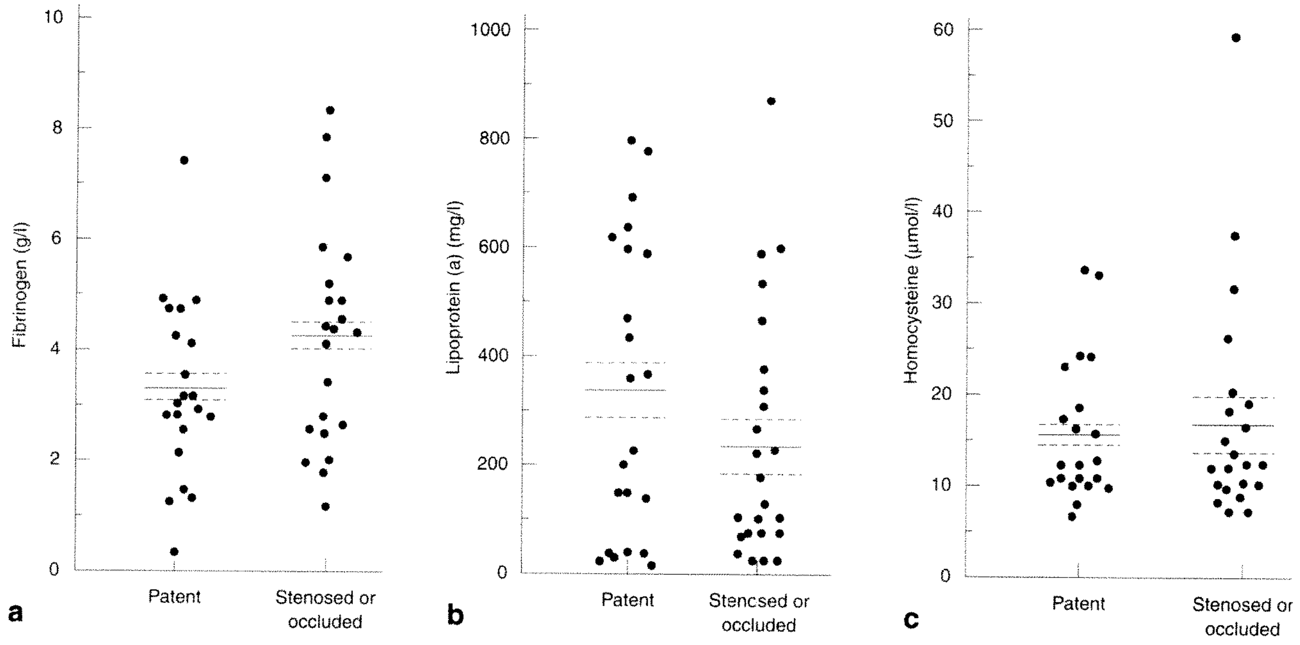

Fig. 2 Association between **a** plasma fibrinogen, **b** serum lipoprotein (a) and **c** plasma homocysteine levels, and outcome following infrainguinal arterial reconstruction with vein. Solid lines represent the mean and broken lines the s.e.m. There were no significant differences

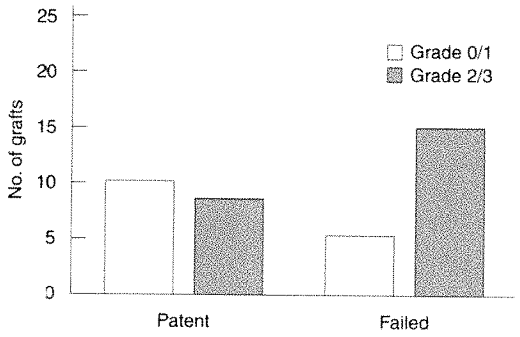

Fig. 3 Influence of pre-existing histological grade on outcome following infrainguinal bypass. $\chi^2 = 3{\cdot}25$, 1 d.f., $P = 0{\cdot}07$

presence of a 'failed' graft, but this difference just failed to achieve significance (4·2(0·4) *versus* 3·2(0·3) g/l; $n = 45$, $P = 0{\cdot}09$). Patients with a raised fibrinogen level were no more likely to develop graft occlusion or stenosis before the median time to failure of 6 months than those without ($\chi^2 = 0{\cdot}54$, 1 d.f., $P = 0{\cdot}31$).

A total of 39 grafts for which both the outcome and the morphological characteristics of the vein before bypass were known were available for analysis. Nineteen grafts remained patent of which 15 had grade 0/I pre-existing IH. Twenty grafts thrombosed or developed a stenosis, of which 13 had grade II/III pre-existing IH. The presence of pre-existing IH was thus found to be predictive of outcome following infrainguinal reconstruction ($\chi^2 = 7{\cdot}72$, 1 d.f., $P = 0{\cdot}006$). Grafts exhibiting grade II/III pre-existing disease were significantly more likely to fail within 6 months of operation than those without ($\chi^2 = 4{\cdot}57$, 1 d.f., $P = 0{\cdot}03$). When the scoring system incorporating muscle hypertrophy was used in place of a simple estimation of intimal thickness, the relationship between vein morphology and outcome was not significant (*Fig. 3*).

Discussion

For the purposes of this study, a graft was deemed to have 'failed' when a stenosis of 50 per cent or greater was found on duplex surveillance, or where the graft had occluded. This is somewhat controversial as the evidence that a graft with a 50 per cent stenosis will necessarily fail is weak. However, the aim of duplex imaging is to identify a graft 'at risk' before it occludes and, for the purposes of this study, the chosen criteria for failure were felt to be justified. Of the 19 grafts that were deemed to have a stenosis, 17 underwent secondary procedures whereas only one of the five that occluded had further surgery.

Homocysteine is a thiol-containing amino acid resulting from methionine metabolism. Homocysteinaemia is an autosomal recessive error of this metabolic pathway, most commonly due to a deficiency of the enzyme cystathionine β synthase[25]. Homozygotes usually succumb to the complications of cardiovascular disease but heterozygotes, accounting for one in 70 of the population, are much less severely affected[26]. Mild homocysteinaemia may be caused by deficiencies of vitamins B_6, B_{12} and folate and these are easily treated. Patients with cystathionine β synthase deficiency fall into two groups; those responsive to supplementation and those unresponsive[27].

Since McCully[28] first suggested a link between homocysteinaemia and arteriosclerosis, firm evidence of a link between homocysteine and ischaemic heart disease[29–31] and peripheral vascular disease[16,32] has been reported.

The prevalence of homocysteinaemia (57 per cent) in this study was much higher than the reported figures of up to 38 per cent in groups at risk of peripheral vascular disease[33,34]. The patients, however, had advanced disease and this prevalence figure is similar to that reported by Irvine *et al.*[23]. This study reinforces the importance of homocysteinaemia as a risk factor for lower limb arterial disease.

The identification of a significant association between homocysteinaemia and the presence of pre-existing IH in vein is not surprising. Despite this, the study did not reveal a correlation between raised plasma homocysteine level and graft failure. No other prospective series has examined this issue, although one retrospective case–control study suggested that homocysteinaemia is a risk factor for vein graft stenosis[23]. The present results are supported by those of Eritsland *et al.*[22], who found no effect of homocysteinaemia following coronary artery bypass grafting. The association between raised homocysteine levels and pre-existing vein hyperplasia but not graft failure suggests that homocysteinaemia might predispose to mild IH only. There was in fact no association between hyperhomocysteinaemia and grade of IH; hyperhomocysteinaemia appeared to be associated with the progressive development of IH in vein.

Fibrinogen is the soluble precursor of fibrin, increasing platelet aggregation[35], and is chemotactic and mitogenic to smooth muscle cells[36–38]. These processes are both involved in the formation of atherosclerotic plaques, and hyperfibrinogenaemia has been associated with both ischaemic heart disease[39,40] and peripheral vascular disease[41,42].

At least three series have reported an association between plasma fibrinogen and vein graft stenosis[19–21]. Despite this, an association between plasma fibrinogen and the presence of pre-existing IH has not been shown in the present study. The mean plasma fibrinogen level in patients with graft 'failure' was higher than that in patients with a patent graft, but this difference narrowly failed to reach significance. This does not detract from the findings of previous studies, and may represent a type II statistical anomaly.

The findings with respect to lipoprotein (a) are notable. Raised levels of serum lipoprotein (a) have been associated with coronary artery disease, myocardial infarction and peripheral vascular disease, and may be associated with disease severity[17,18,43–45]. Reports regarding the role of lipoprotein (a) in vein graft stenosis are contradictory, however, with two series showing an association after cardiac bypass[46,47], while another reported an unexplained excess of graft failures in the lowest quartile of levels recorded[22]. Few studies have assessed the impact of lipoprotein (a) following peripheral vascular reconstruction. One prospective study reported an association[21], this being contradicted by a case–control study showing lower levels of lipoprotein (a) in patients with a failed graft[23].

In this series the mean serum lipoprotein (a) for all patients was just below the 95th centile for the normal population. Twenty-three patients (57 per cent) had levels above this, supporting the observation that hyperlipoproteinaemia is a risk factor for peripheral vascular disease. It is surprising therefore that lipoprotein (a) levels were lower both in those with pre-existing IH and in those whose grafts 'failed', although only significantly in the former. These results lend support to the hypothesis that lipoprotein (a) is not a significant factor in vein graft stenosis.

The concept of assessing vein quality in order to predict the outcome of arterial revascularization is an attractive one. The processes involved in the development of pre-existing venous IH and postbypass neointimal hyperplasia are similar and the latter may merely represent an ongoing disease process. The changes that encompass the phenomenon of pre-existing IH, namely endothelial discontinuity, a thickening of the intima and media, and the appearance of intimal smooth muscle cells, were reported by Panetta *et al.*[48]. Since then a number of clinicians have demonstrated an association between prebypass intimal thickness and vein graft failure[11,49]. In these series, semiquantitative techniques of intimal assessment were employed, but the association has been disputed recently in a study in which image analysis methods for intimal quantification were used[12]. It was noted in this series that extensive intimal changes were found in only a small number of veins.

In the cohort reported here 23 (42 per cent) of 54 patients had grade II or III pre-existing IH, considerably higher than the incidence reported in other series. A highly significant association between the presence of severe pre-existing IH and subsequent vein graft failure was shown in the present study.

In summary, this series has reaffirmed the association between plasma homocysteine and serum lipoprotein (a) levels and the development of atherosclerotic disease. An association between plasma homocysteine and pre-existing IH has been identified and the results suggest a raised level of lipoprotein (a) to be protective against the development of pre-existing IH. It has been reaffirmed that significant pre-existing IH in saphenous vein is associated with a poor outcome after infrainguinal bypass grafting and these results lend support to the association between plasma hyperfibrinogenaemia and graft failure.

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Original article

Surgery may be curative for patients with a localized perforation of rectal carcinoma

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Background: Perforation at the time of operation adversely affects the prognosis of rectal cancer. These procedures have been termed 'palliative' or 'non-curative'. The long-term outcome of generalized perforations may be different from that of localized or contained perforations. Although the oncological results may be compromised when the tumour is perforated, results in cases where the perforation is contained may not be as bad as previously thought. An attempt was made to examine the intermediate and long-term results for locally contained perforated rectal cancers.

Methods: Some 848 patients with rectal cancer were operated on between March 1989 and December 1995. Of these, 42 (5 per cent) had a locally contained perforation of the rectum. Median follow-up was 23 (range 12–74) months.

Results: The survival of patients with locally contained tumour perforation who underwent resection without macroscopic residual disease (40 per cent at 5 years) was significantly better than that of patients with metastatic disease at the time of surgery (zero at 4 years) ($P < 0{\cdot}01$). The survival of patients in whom the tumour was inadvertently perforated during operation was similar to that of patients with locally contained spontaneous tumour perforations. The incidence of local recurrence in these perforated cases was low provided that a wide tumour clearance was achievable at the time of operation. Operative mortality and morbidity rates were not significantly different but the incidence of postoperative wound infection was marginally higher among patients with perforation.

Conclusion: If clear margins can be obtained at the time of operation the prognosis of locally contained perforated rectal cancers is good and approaches that of a potentially curative resection.

Paper accepted 4 June 1999

British Journal of Surgery 1999, 86, 1448–1450

Introduction

Despite advances in the management of colorectal cancer, a significant number of patients still present late. It is well known that it is difficult to differentiate between adhesions and tumour invasion. Wide resection with *en bloc* resection of adjacent organs where necessary therefore has been advocated[1,2]. It is thought that tumour cells spilled into the abdominal cavity may result in a poorer prognosis. These procedures are therefore deemed palliative and classified together with metastatic disease[3–9]. When tumours are locally aggressive, a locally contained perforation may arise. Most of the relevant reports are more than 10 years old and retrospective[3–9]. In the present study, the prognosis of patients with minimal tumour spillage was compared with that of patients with generalized perforation or metastatic disease.

Patients and methods

Some 848 patients with rectal cancer underwent operation in this department between March 1989 and December 1995. Data on patient demographics; tumour size; resection margins; the presence of locally contained or generalized perforations; histology; postoperative complications including anastomotic dehiscence, abdominal sepsis, wound infections, chest and urinary infections; were collected and entered prospectively into a customized computerized database.

A locally contained tumour perforation was defined as tumour perforation localized in the pelvis or occurring at the time of surgery without generalized spillage. Patients with perforations remote from the tumour were excluded from this study. Generalized perforation was tumour perforation with generalized contamination of the peritoneal cavity.

The histology was read by a single pathologist and staged using the Astler–Coller modification of Dukes classification. Patients with locally contained tumour perforation were classified by depth of invasion and lymph node status into Dukes stage A, B, C and 'D'.

Patients were followed every 3 months for 2 years, 6 monthly for the next 2 years and annually thereafter. At each visit a full examination was carried out, a questionnaire was completed and the carcinoembryonic antigen concentration in serum was assayed. Patients who did not attend follow-up appointments were recalled by telephone and mail.

Mortality data were collected from a combination of inpatient deaths, obituaries in the national papers, telephone contact on failure to attend appointments and National Cancer Registry data. The cause of death was ascertained from the inpatient data or the death certificates. Perioperative death was defined as death occurring within 30 days of operation.

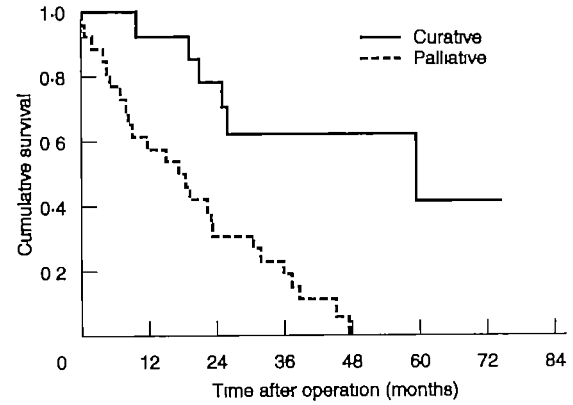
Local recurrence was defined as radiological or pathological evidence of recurrent pelvic or perineal tumour before death. The date of local recurrence was defined as the first new clinical or histological evidence of local recurrence.

Kaplan–Meier survival curves were constructed and tests of significance were done using the log rank test and χ^2 or Fisher's exact test.

Results

Of 848 patients, 16 were lost to follow-up. Locally contained tumour perforation occurred in 42 patients (5 per cent). This group formed the cohort for the analysis. Tumour planes were perforated accidentally during pelvic dissection in ten patients and spontaneous tumour perforation occurred in 32. In these patients all local tumour was removed macroscopically through a wide dissection and total mesorectal excision. There were 31 men and 11 women with a median age of 66 (range 28–86) years. Median follow-up was 23 (range 12–74) months. All of these patients were offered adjuvant postoperative chemoradiotherapy.

Most patients had locally advanced disease (T_3, T_4) and there were no T_1 lesions in this cohort. Twenty-seven of 42 also presented with metastatic disease compared with 233 (29 per cent) of the remaining patients with rectal cancer ($P < 0{\cdot}01$). The operative morbidity rate in the two groups was not significantly different. After operation for perforated rectal cancer, there were six patients with wound infection, two with fistula and one each with anastomotic leak and chest infection (overall complication rate 12 per cent). In those without perforation there were 169 complications (14 per cent), including wound infection and burst abdomen, anastomotic leak, chest infection, abdominal sepsis, intraoperative transfusion, fistula formation, acute myocardial infection, cerebrovascular accident, deep venous thrombosis and pulmonary embolism.



No at risk							
Curative	15	13	10	6	5	2	1
Palliative	27	15	8	5	0	0	0

Fig. 1 Survival curves for patients with perforated cancer who underwent potentially curative resection or who had metastatic disease

The 15 patients with localized perforation who underwent potentially curative resection had a significantly better crude 5-year survival rate than the 27 patients who had perforation and metastatic disease at the time of surgery ($P < 0{\cdot}01$) (*Fig. 1*). The survival curve of the latter was similar to that of patients with Dukes 'D' non-perforated tumours, while that of the patients without metastases was similar to that of those who underwent curative resection but did not have tumour perforation (5 year survival rate 58 per cent).

Local recurrence at the last follow-up was similar, affecting 46 patients (8 per cent) in the non-perforated group and one (7 per cent) in the perforated group (who initially underwent curative resection).

Discussion

A hundred years ago Lack[1] observed the phenomenon of tumour implantation and recurrence. Following this, *en bloc* resection of tumours was advocated by Ryall[2] in 1908, and is still a very sound surgical principle today. As it is often almost impossible to differentiate between inflammatory adhesions and tumour infiltration, most surgeons would err on the side of safety and perform *en bloc* resection. In the presence of tumour perforation, tumour cells may spread transcoelomically and this had been shown to increase local recurrence and decrease survival rates[3–9]. As a result of these reports of a poorer prognosis[10,11] for patients with perforated tumours, surgery in these patients has been classified as palliative. Some centres have grouped these tumours together with metastatic tumours as Dukes 'D' lesions. While this may be true in a patient who has gross dissemination, patients with locally contained tumours may not have such a dismal prognosis.

In the latter group, great care should be taken to ensure that a potentially curative resection is performed. Attention should be paid to locally contained perforated rectal tumours to ensure that the radial margins are free of tumour and to avoid leaving gross macroscopic disease in the pelvis. Tumoricidal solutions may be instilled intraperitoneally and intraluminally[12] after cross-clamping below the tumour before constructing the anastomosis. Patients with locally perforated tumours were routinely referred for adjuvant chemotherapy and radiotherapy.

These patients are a select group with locally contained perforated tumours that macroscopically have been resected completely. Patients with generalized and gross perforation, in whom the chance of diffuse intraperitoneal spread was obviously higher, were not considered in this series. The incidence of localized tumour perforation was 5 per cent, compared with the value of 26 per cent reported by Ranbarger *et al.*[3] for all perforated tumours. Contained perforation, whether spontaneous or iatrogenic, did not make a difference in survival. The crude survival rates for the two groups were similar.

Tumours that perforate locally seem to be much more aggressive than other rectal cancers as a significantly larger proportion of these patients had metastatic disease at the time of diagnosis (27 (64 per cent) of 42 *versus* 233 (29 per cent) of 790). Survival in patients with locally contained perforated rectal cancer is very much dependent on the presence of metastatic disease. In the absence of the latter, if a wide margin clear of all macroscopic tumour is achieved, the survival curve approximates that of patients with a non-perforated tumour.

It is concluded that locally contained perforations of the tumour in rectal cancer surgery can be treated with low mortality and morbidity rates. Good survival rates and low local recurrence rates can be obtained if all macroscopic disease is removed.

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Original article

Experimental study of neorectal physiology after formation of a transverse coloplasty pouch

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Background: A novel transverse coloplasty pouch (TCP) with a larger neorectal volume than a straight coloanal anastomosis (CAA) but a smaller volume than a short colonic J pouch (CJP) may improve short-term function after rectal excision.

Methods: Twelve pigs were investigated 6 weeks after complete rectal excision followed by reconstruction with a CAA, CJP or TCP. The results were compared with findings in the normal pig rectum.

Results: The colonic transit times assessed by radio-opaque marker transit were 24 h for CAA, 60 h for CJP and 32 h for TCP. Non-operated control pigs had a mean transit time of 46 h. Pigs that had a CJP developed colonic dilatation and substantial faecal impaction. Colonic electrostimulation induced an adaptive relaxation in the normal rectum but a pressure increase in all neorecta, particularly after CAA. The neorectal longitudinal smooth muscle layer in pigs with a TCP was significantly thicker than that in pigs with a CAA or CJP; its thickness was closest to that of the normal pig rectum. Colonic smooth muscle layers 10 cm proximal to the coloanal anastomosis, above the neorecta, were significantly thicker after CJP than after CAA or TCP formation. No significant difference in microcirculation was observed between the three restorative procedures.

Conclusion: Accelerated colonic transit and a lack of adequate relaxation upon endoluminal pressure increase was associated with urgency and incontinence after CAA. Delayed colonic transit, faecal impaction and ineffective muscular hypertrophy due to pouch dilatation and constipation indicated evacuation problems after CJP construction. Functional and morphometric data for TCPs suggested almost normal defaecation. Of the three restorative procedures, the data for TCPs were most similar to those obtained in the normal pig rectum at short-term follow-up.

Presented in part to the annual meetings of the American Gastroenterology Association, Washington DC, USA, May 1997 and the Swiss Surgical Society, Davos, Switzerland, June 1997, and published in abstract form as *Gastroenterology* 1997; **112:** A1487 and *Swiss Surgery* 1997; 8(Suppl 1). A4 02

Paper accepted 20 June 1999

British Journal of Surgery 1999, **86**, 1451–1458

Introduction

Anal anastomosis with a colonic J pouch (CJP) is one of the standard reconstructions after complete rectal excision. CJP construction results in good short-term function, but 10–30 per cent of patients have long-term impairment such as difficult pouch evacuation, stool fragmentation and/or constipation[1–4]. These dysfunctions are encountered particularly if the length of the J pouch is greater than 5–6 cm[2,5] or in elderly patients[6], and seem also to depend on the colonic segment used for reconstruction[7]. In contrast, reconstructions with a straight coloanal anastomosis (CAA) are accompanied by urgency, frequent bowel movements, soiling and even incontinence, although this improves 6–24 months after surgery[2,8,9].

The optimal procedure for rectal reconstruction would include improved short-term function but would avoid the long-term dysfunction associated with a CJP. In this study, a novel transverse coloplasty pouch (TCP) similar to a pyloroplasty or a strictureplasty was constructed in pigs (*Fig. 1*). This pouch is technically simpler than a CJP and provides a 40 per cent increase in volume compared with a

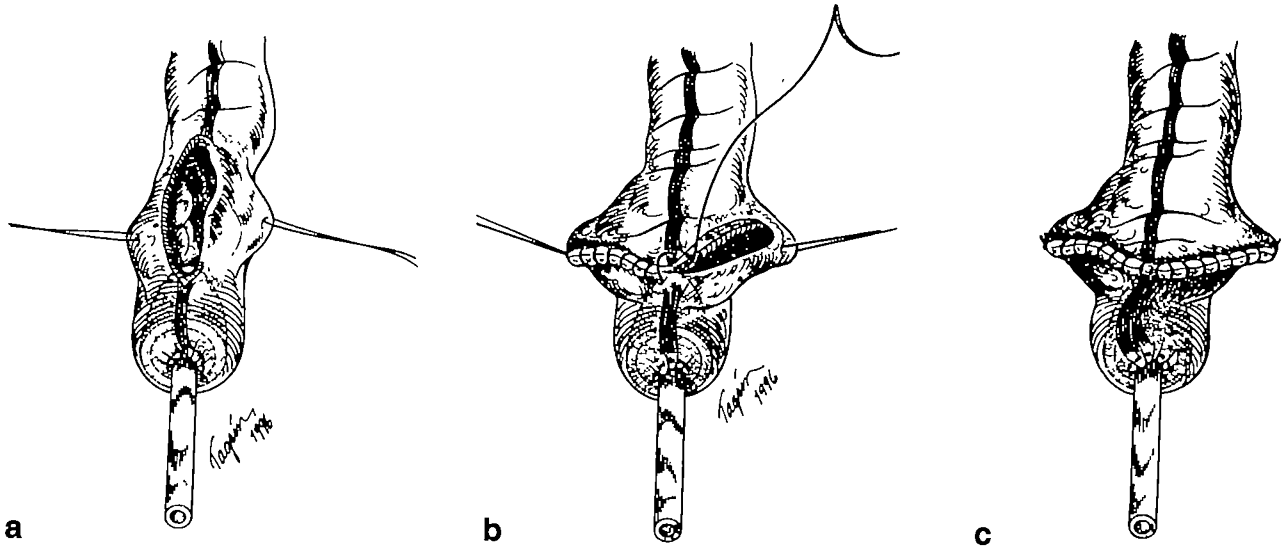

Fig. 1 Design of the novel transverse coloplasty pouch.
a Some 2 cm above the tip of the transected sigmoid stump already bearing the anvil, a 4-cm longitudinal incision is performed along the taenia coli.
b and **c** Stay sutures are placed and the colon is closed transversely by means of an extramucosal running suture
(From *Surgery* 1999; **125**: 105-12. Reproduced with permission from Mosby, St Louis, Missouri, USA)

neorectum after CAA. Furthermore, the TCP demonstrated better short-term function than CJP and CAA reconstructions after complete rectal excision[10,11].

The aim of the study was to find a rationale for the functional differences observed in pigs after CAA, CJP and TCP reconstruction, and to relate the results to findings in the normal pig rectum.

Materials and methods

Animals and surgical procedures

Twenty-one pigs supplied by a commercial breeder and aged 12–16 weeks with a median weight of 20·8 (range 17–26) kg were used. The first week after the surgical intervention the animals were held in single cages at the university's veterinary clinic. They were then transported to a specialized farm for research animals. The study was approved by the state's ethics committee on animal research.

Six pigs were used in a preliminary study to establish the operative techniques and investigative procedures. The remaining 15 pigs were assigned randomly to one of the three reconstructive procedures following complete rectal resection, as described in detail previously[10]. Briefly, under general anaesthesia a complete rectal mobilization was performed through an abdominal midline incision down to the pelvic floor, preserving the autonomic nerves. The rectal excision was completed by transanal circular division of the anal mucosa and the internal anal sphincter 0·5 cm proximal to the dentate line, as well as at the colorectal junction 12 cm above the anal verge. An anal purse-string suture was prepared. The three types of rectal reconstruction used were a straight CAA, a 4-cm CJP or a TCP. The latter pouch was formed by opening the colon along the taenia coli over a distance of 4 cm. Stay sutures were placed in the middle of the cut edges, and the longitudinal opening was then closed transversely by a seromuscular running suture (*Fig. 1*). A stapled anastomosis (21-mm ILS circular stapler; Ethicon Endosurgery, Cincinnati, Ohio, USA) was used in all three groups to restore bowel continuity. The anastomosis was placed at or within 0·5 cm of the dentate line.

Three pigs died, from small bowel obstruction, extended wound infection and myelomeningitis. In the 12 surviving pigs (four in each group) physiological investigations were performed 6 weeks after rectal reconstruction. The pigs were killed by intracardiac potassium injection, after which the neorectum was excised *in toto*, together with the anus and part of the left hemicolon, and sent for histological examination.

Radio-opaque marker transit and colonic transit time

For determination of colonic transit times, gelatin capsules, each containing ten radio-opaque polyurethane markers consisting of 40 per cent barium sulphate US Pharmacopoeia (to Food and Drug Administration specification) (Fa.P. and A. Mauch, Münchenstein, Switzerland), were used. Seventy-two hours before death, a total of six capsules was given to each pig, with 12-h intervals between each capsule. Twelve hours after intake of the last capsule abdominal radiographs were obtained. The number and distribution of the remaining markers were determined. Colonic transit times were calculated according to the formula of Metcalf *et al.*[12] as the number of visible markers × time between capsule intake/number of markers per capsule, i.e. colonic transit time in hours = number of markers × 1·2.

Five non-operated pigs served as controls. They had a normal rectum *in situ* and received the same food and the same number of markers.

Rectal and neorectal manometry with and without colonic electrostimulation

A rectosphincteric manometry balloon probe (Schuster probe; Sandhill Scientific, Highlands Ranch, Colorado, USA) was inserted transanally into the rectum/neorectum before its mobilization. The intrarectal balloon was filled with 25 ml air and pulled back to stop at the proximal end of the anal canal. The colon was closed by a clamp 15 cm proximal to the anal verge. Contractions and relaxations of the rectum/neorectum were registered by transmission of pressure alterations within the balloon to a transducer connected to a chart recorder (Vagorec 5; Institut Straumann, Waldenburg, Switzerland), analogous to the gastric manometry technique during vagotomy described by Burge and Vane[13]. The chart speed was 1 mm/s. Electrostimulation was delivered by an integrated current generator connected to a double ring electrode that was fitted around the colon 12 cm proximal to the anal verge. The colon was stimulated with 120 mA for intervals of 30 s. Manometry with and without electrostimulation was performed in the normal rectum before rectal excision and 6 weeks after operation in the neorecta (CAA, CJP and TCP).

Laser Doppler flow measurements

Colonic blood flow was assessed with a laser Doppler flow (LDF) probe (fibre separation 0·25 mm; probe PF 408; Perimed, Jarfäla, Sweden). Flow measurements were monitored on a Periflux 4001 Master (Perimed) and expressed as perfusion units, as described previously[14]. In brief, light generated by a laser diode (780 nm wavelength with maximum emission energy of 0·8 mW) penetrated the tissue where it was reflected by circulating blood cells. The reflected light was returned via an optical fibre to a photodetector in the instrument and transformed into an electrical signal. The electrical signal was proportional to the product of the number of blood cells moving in the measured volume and the mean velocity of the cells, and was referred to as blood flux. Analogue LDF signals were digitalized with a UIM 100 (Biopac, Goletta, California, USA) and processed on a personal computer with the software provided (MP 100 WSW; Biopac). A vertical trans-symphysis access to the neorectum allowed *in situ* LDF measurements to be made. The probe was placed in a probe holder to avoid pressure on the tissue. LDF measurements were made in all pigs at the antimesenteric border of the neorectum at 1, 4 and 8 cm proximal to the former colonic cut edge. The 4-cm point was therefore located at the apex of the CJP. The measurements were repeated three to five times. The LDF values were largely reproducible except when the probe lay directly on an artery giving falsely high values.

Histopathology

The specimens of rectum and the anoneorectosigmoid colon were immediately opened and fixed in formalin without stretching to avoid an investigator bias for the measurement of bowel wall thickness. From each neorectal specimen, four longitudinal tissue samples comprising all bowel wall layers were taken, two at 3 cm and two at 10 cm proximal to the anastomosis; these were embedded in paraffin. In pigs with a CJP or TCP the 3-cm location represented tissue samples within the pouch. The 10-cm point was located in the colon, always above the neorectum. Six normal rectal specimens served as controls. Sections of 5 µm were stained with haematoxylin and eosin, according to the method of van Gieson. The thickness of the mucosa and of the circular and the longitudinal smooth muscle layer was measured microscopically using a morphometric–densitometric software package (Diasys II; Datalab, Thörigen, Switzerland). The observer was blinded to the type of restorative procedure and unaware of the other study results.

Statistical analysis

Results were expressed as mean(s.e.m.). Differences in the non-parametric, unpaired variables among the three groups of restorative procedures were analysed with the Kruskal–Wallis test, and differences between two of the three groups were analysed with the Mann–Whitney *U* test. The paired non-parametric Wilcoxon signed rank test was used to compare data obtained from all neorecta or one type of neorectum with those from the normal rectum in the same pigs. Statistical significance was attributed at the 5 per cent level. Winstat (version 5.3; Microsoft, Redmond, Washington, USA) served as the computerized statistical analysis package.

Results

Radio-opaque marker transit and colonic transit time

Three days after the beginning of marker intake, conventional abdominal radiographs of the pig abdomens demonstrated a mean(s.e.m.) of 20(6) residual radio-opaque markers after CAA, 50(8) after CJP and 27(4) after TCP construction. The calculated mean(s.e.m.) transit times were 24(7), 60(10) and 32(4) h respectively. The transit time in pigs with a CJP was significantly longer than that in pigs with a CAA ($P < 0{\cdot}04$) or TCP ($P < 0{\cdot}04$). The difference between TCP and CAA reconstructions was not significant ($P > 0{\cdot}2$). In pigs with a CAA or TCP the radio-opaque markers were distributed through the entire large bowel, whereas pigs with a CJP accumulated the markers in the colonic segment proximal to the pouch (*Fig. 2*). Furthermore, all animals with a CJP had colonic dilatation with faecal impaction, predominantly in the descending colon (*Fig. 2*). In a control group of non-operated pigs the mean(s.e.m.) number of markers was 38(4) and the transit time was 46(5) h.

Rectal and neorectal manometry with and without colonic electrostimulation

Under general anaesthesia none of the normal recta showed endoluminal pressure alterations (*Fig. 3a*). In contrast, all neorecta exhibited spontaneous pressure increases of 48(8) mmH$_2$O, lasting 30–50 s, every 1–3 min (*Fig. 3b*). Electrostimulation of the sigmoid colon decreased the mean(s.e.m.) pressure in the normal rectum by 10(6) mmH$_2$O (*Fig. 3c*), but increased the pressure in rectal reconstructions by 23(5) mmH$_2$O (*Fig. 3d*). This stimulated pressure change in the neorectum was significantly different from that in the normal rectum ($P < 0{\cdot}005$).

The increase in spontaneous endoluminal pressure was 39(6) mmH$_2$O for CAA, 70(26) mmH$_2$O for CJP and 29(10) mmH$_2$O for TCP construction ($P > 0{\cdot}4$). On electrostimulation, the increase was 33(9), 19(17) and 18(7) mmH$_2$O respectively ($P > 0{\cdot}5$). There was no significant difference in stimulated pressure increase between CAA and either type of pouch ($P > 0{\cdot}1$, Mann–Whitney *U* test).

Histological measurements of bowel wall layers

The mean(s.e.m.) thickness of the mucosa measured 3 cm proximal to the anastomosis was 670(20) µm after CAA, 690(60) µm after CJP and 800(110) µm after TCP formation ($P > 0{\cdot}4$); at 10 cm it was 610(40), 680(50) and 660(40) µm respectively ($P > 0{\cdot}8$). The mucosa of the

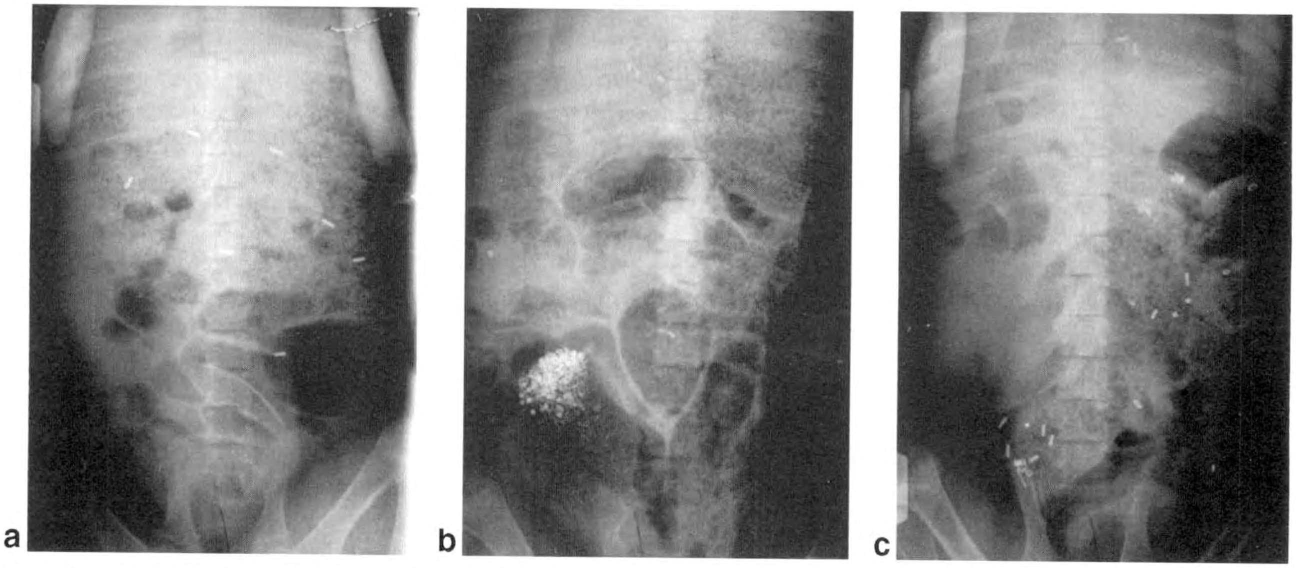

Fig. 2 Supine anteroposterior abdominal radiographs showing radio-opaque markers. After **a** straight coloanal anastomosis and **c** transverse coloplasty pouch construction there is a ubiquitous distribution of a limited number of markers in the colon, whereas after **b** colonic J pouch formation there is colonic obstruction with an accumulation of markers above the pouch (within sigmoid loop to the right hand of the pig)

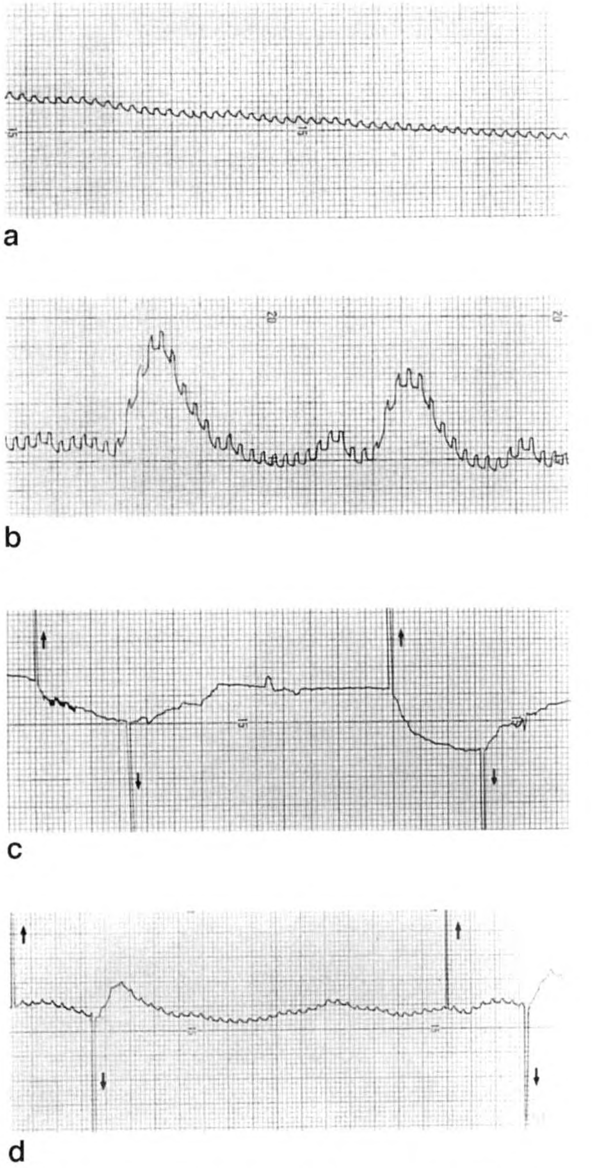

Fig. 3 Rectal and neorectal pressure changes with and without colonic electrostimulation. Time is plotted on the x-axis (smallest square represents 2 s) and pressure on the y-axis (smallest square represents 1 mmH_2O).

a The normal pig rectum showed no spontaneous contractions under general anaesthesia.

b In contrast, in all the neorecta (example shown for a transverse coloplasty pouch (TCP)) the endoluminal pressure increased periodically every 1–3 min.

c Following colonic electrostimulation 12 cm above the anal verge, the normal rectum reacted with relaxation and a pressure decrease, whereas the neorectum (example shown for a TCP) showed a pressure increase (**d**) which was smaller than the spontaneous one (**b**).

Spikes with arrows pointing upwards indicate the beginning of stimulation and spikes with arrows pointing downwards denote the end of stimulation

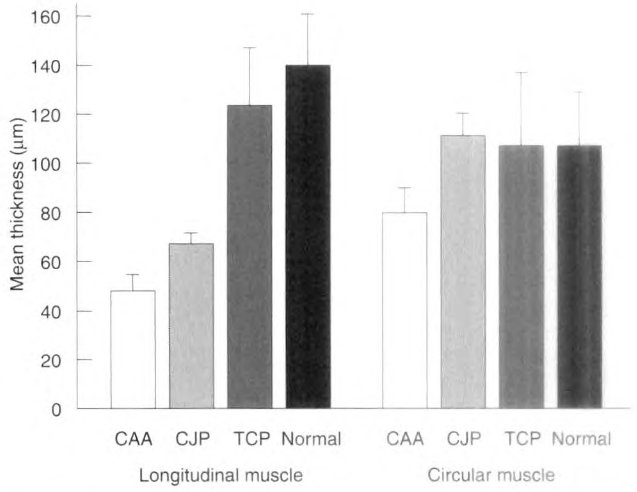

Fig. 4 Mean(s.e.m.) thickness of longitudinal and circular smooth muscle layers 3 cm above the coloanal anastomosis after three different restorative procedures and above the dentate line in normal rectum. CAA, straight coloanal anastomosis; CJP, colonic J pouch; TCP, transverse coloplasty pouch

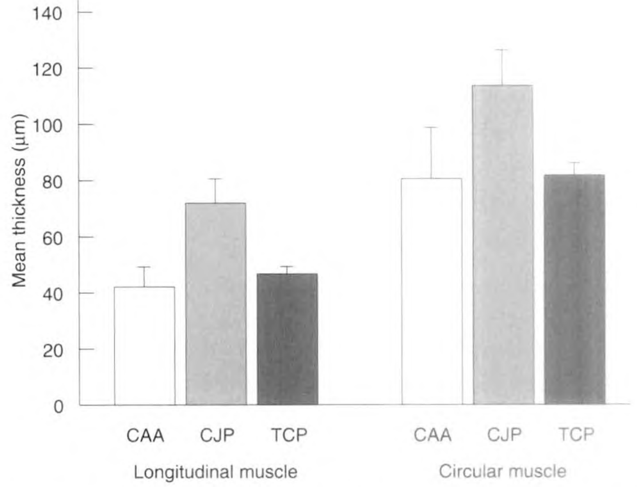

Fig. 5 Mean(s.e.m.) thickness of longitudinal and circular smooth muscle layers of the colon 10 cm above the coloanal anastomosis (proximal to the three different reconstructions). CAA, straight coloanal anastomosis; CJP, colonic J pouch; TCP, transverse coloplasty pouch

normal rectum measured only 470(20) µm and was significantly thinner than that found in all three types of neorectum ($P < 0{\cdot}001$).

The mean thicknesses of the longitudinal and circular smooth muscle layers in the neorectum 3 cm above the coloanal anastomosis are summarized and compared with those in normal rectum in *Fig. 4*. The longitudinal muscle

Table 1 Colonic laser Doppler blood flow measurements 1, 4 and 8 cm proximal to the coloanal anastomosis 6 weeks after rectal reconstruction

	Laser Doppler flux (perfusion units)		
	1 cm	4 cm	8 cm
Coloanal anastomosis	30(8)	52(7)	75(9)
Colonic J pouch	59(28)	81(27)	110(24)
Transverse coloplasty pouch	68(16)	89(6)	104(12)

Values are mean(s.e.m.). $P > 0.1$ (Kruskal–Wallis test)

layer was significantly thicker after reconstruction with a TCP than a CAA ($P < 0.01$) or a CJP ($P < 0.02$) and, in contrast to that after CAA and CJP formation, was comparable to that in the normal rectum ($P > 0.2$). The thickness of the circular smooth muscle at 3 cm was similar in all groups; the only significant difference was found between CAA and CJP construction ($P < 0.04$).

Fig. 5 shows smooth muscle thicknesses in the colon at 10 cm proximal to the coloanal anastomosis, i.e. above the neorectum. CJP construction resulted in a significantly thicker longitudinal muscle layer than that observed in pigs with a CAA ($P < 0.01$) or TCP ($P < 0.01$); the latter two were comparable ($P > 0.3$). The circular smooth muscle at 10 cm above the anastomosis was significantly thicker after CJP than CAA ($P < 0.05$) or TCP ($P < 0.03$) formation.

Laser Doppler flow measurements

The neorectal microcirculatory blood flow was assessed by laser Doppler flowmetry to clarify whether differences in microcirculation contributed to the functional and morphological variations. The mean perfusion values after CAA, CJP and TCP construction, measured at 1, 4 and 8 cm proximal to the resection margin, are summarized in *Table 1*. Microcirculatory blood flow did not differ in the three groups at either 1 cm ($P > 0.2$), 4 cm ($P > 0.2$) or 8 cm ($P > 0.1$) (Kruskal–Wallis test). However, comparison of CAA with CJP alone revealed a significantly reduced microcirculation 8 cm above the coloanal anastomosis after CAA ($P < 0.05$, Mann–Whitney U test). Similarly, microcirculatory blood flow was lower after CAA than after TCP formation at both 1 cm ($P < 0.03$) and 4 cm ($P < 0.03$).

Discussion

Recent advances in rectal cancer surgery have increased the rate of sphincter preservation and the use of coloanal and very low colorectal anastomosis[15,16]. The two most frequently performed rectal reconstructions, the straight CAA and the CJP, both have functional disadvantages[2,4,17]. Oversize of the reservoir and/or neutralization of pro-peristaltic force vectors seem to be important in the pathophysiology of CJP malfunction[1,18,19]. Considering that even small CJPs of 5–6 cm in length have impaired function[5], the optimal reservoir size may lie between that of a CAA and a CJP. The TCP meets this criterion, and excellent short-term function has been demonstrated in pigs with this novel pouch[10,11]. The present study investigated the physiology of these three groups of pigs, and their associated differences were related to the observed functional changes.

The moderately decreased colonic transit time after TCP construction compared with CAA may be an advantage, and reduce urgency and incontinence. In contrast, the significantly delayed colonic transit time associated with CJP formation, with substantial faecal impaction and marker accumulation, shows similarities to the known evacuation problems of human CJPs. Marker accumulation above, rather than in, the CJP is the result of relative pouch obstruction. The colon above the pouch was not inhibited, as the histomorphological investigations showed. Although a small pouch of 4 cm length was chosen in this series, the findings in pigs cannot be correlated directly to those in humans with a small CJP since there are species differences in colonic diameter[5].

Normal pig rectum under general anaesthesia showed stable manometry values and hence a phase lacking peristalsis, as reported by Couturier *et al.*[20]. Electrostimulation of the sigmoid colon in the present study decreased the endorectal baseline pressure. This accommodation response probably reflected a receptive relaxation of the rectal ampulla avoiding urgency in response to faeces that were transported into the rectum[21,22]. In contrast to normal rectum, all three types of neorectum exhibited baseline peristalsis with a cyclical increase in endoluminal pressure. Since the neorectum consisted of sigmoid colon, which is different from rectum with respect to neuromuscular anatomy and physiology, some peristalsis of this bowel segment was expected during sleep. However, during colonic electrostimulation there was a reduced peak of neorectal pressure in comparison with the spontaneous activity. This finding may reflect a partial adaptation of the neorectum corresponding to the development of a reservoir function by 6 weeks after operation. The smallest accommodation in colonic pressure increase was noted after CAA. The lack of an adequate accommodation response in CAA may be a result of its small neorectal volume and helps to explain why restoration of bowel continuity by CAA is often accompanied by urgency[21,23].

Peristalsis is the result of coordinated synchronous movements of the longitudinal and circular smooth muscles in the distal pig colon[24]. The longitudinal muscle provides a vector of force along the intestine and contributes substantially to propulsion of the intestinal content[24]. The quantification of colonic smooth muscle thickness and its correlation to the clinical findings is a new approach to the investigation of defaecation disorders. After TCP formation, the neorectal longitudinal smooth muscle was significantly thicker than that after reconstruction with a CAA or CJP. The observed muscular hypertrophy seems to favour undisturbed defaecation in pigs with a TCP[10]. The lack of hypertrophy of the colonic smooth muscles proximal to the TCP gives additional evidence of undisturbed evacuation with this pouch type. Furthermore, the thickness of the longitudinal and total smooth muscles was closer to that of the normal rectum after TCP than after CAA and CJP construction. Whether similar smooth muscle masses indicate similar defaecatory function is not known. In contrast, neorectal hypertrophy of longitudinal smooth muscles after formation of a CJP was much less obvious than that after TCP construction, although, according to the physical law of Laplace, the larger diameter of a CJP would require even stronger smooth muscles than a TCP for normal defaecation.

The reversed propulsive activity in the J segment may disturb pouch evacuation[1]. The consecutive faecal impaction with pouch dilatation seemed to overstretch the smooth muscles of the CJPs. Their muscular hypertrophy may therefore be less evident and, furthermore, less effective, since an overstretched muscle cannot develop its maximal force. The significant hypertrophy of colonic smooth muscles proximal to the CJP could be interpreted as a partial adaptation to the disturbed pouch evacuation.

The analysis of mucosal thickness showed a significantly thinner mucosa in the normal rectum than in all three types of neorectum. Since the colon proximal to the neorectum exhibited similarly developed mucosa, the thicker mucosa in the neorectum may reflect colonic specificity rather than a consequence of adaptation to facilitate water resorption. Nevertheless, water resorption may be increased after TCP and particularly after CJP reconstructions, both of which provide a larger volume and a larger mucosal surface than CAA[10].

LDF measurements revealed no significant difference in microcirculation between CJPs and TCPs 6 weeks after rectal excision. Functional differences in these two groups cannot be attributed to differences in blood flow[25]. The reduced microcirculation associated with CAA in comparison to the two types of pouch may indicate lower oxygen demand of the significantly thinner smooth muscles[26]. Taken together, it would appear that differences in microcirculation of the total bowel wall are rather the consequence than the cause of differences in morphometry and function.

This study provided physiological evidence that correlated well with the functional advantages of a TCP and with the dysfunction observed after CAA and CJP construction in pigs. None of the rectal reconstructions gained the physiological properties of a normal rectum within the time investigated. Of the three restorative procedures, morphometric and functional data after TCP construction were closest to those of the normal rectum.

Acknowledgements

The authors acknowledge O. Beslac, H. Gisiger and G. Vucic for excellent technical assistance, and S. Grimm for preparing histological sections and assisting in morphometric analysis.

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Original article

Multicentre study of ultrasonographically guided axillary node biopsy in patients with breast cancer

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Background: Axillary lymph node dissection is still performed as a staging procedure since lymph node status is the most important prognostic factor in patients with breast cancer. Sentinel node biopsy may replace routine axillary lymphadenectomy, especially in patients with small breast cancers. This study investigated whether ultrasonographically guided fine-needle aspiration cytology (FNAC) of the axillary lymph nodes in clinically node-negative patients was an accurate staging procedure to select patients for sentinel node biopsy.
Methods: One hundred and eighty-five consecutive patients were included. All had axillary ultrasonography and detected nodes were categorized according to their dimensions and echo patterns. Ultrasonographically guided FNAC was carried out if technically possible. These results were compared with the results of the sentinel node biopsy and subsequent axillary dissection.
Results: In 116 patients no lymph nodes were detected by ultrasonographic imaging. Of 69 patients with visible nodes, 31 had malignant cells on FNAC. There were no false-positive results. Some 87 of 185 patients had axillary metastases on definitive histological examination. Ultrasonography was sensitive in patients with extensive nodal involvement. Failure of the examination was caused by problems learning the method, difficulty in puncturing small lymph nodes and sampling error.
Conclusion: In patients without palpable axillary nodes, a sentinel node biopsy could be avoided in 17 per cent since ultrasonography combined with FNAC had already diagnosed axillary metastases. The method is particularly valuable in larger breast cancers.

Paper accepted 7 June 1999

British Journal of Surgery 1999, 86, 1459–1462

Introduction

The treatment of operable breast cancer consists of radical excision of the tumour or mastectomy combined with complete axillary lymph node dissection. Axillary node status remains the most important prognostic factor in breast cancer. Complete axillary clearance provides the most accurate information about node status but is mostly considered a diagnostic intervention[1–3]. However, it has a significant associated morbidity including lymphoedema, pain, stiffness and weakness of the shoulder[4,5]. In breast cancer it has been demonstrated that a negative sentinel node (the first lymph node draining the primary tumour) indicates that there is no spread to any of the axillary lymph nodes[6–9]. Full axillary lymph node dissection is redundant as a staging procedure for patients with a negative sentinel node.

The disadvantages of sentinel node biopsy are that it is time consuming, the sentinel node cannot always be found (especially in patients with extensive lymph node metastases), there are occasional false-negative results, radioisotopes are needed and frozen-section histological analysis is required. It would be valuable if sentinel node biopsy could be replaced by easier methods.

Bonnema *et al.*[10] evaluated the accuracy of ultrasonography alone and in combination with cytology for detection of axillary metastases in patients with breast cancer and non-palpable lymph nodes. Lymph node metastases were detected by preoperative ultrasonography in combination with cytology in 26 per cent of patients (63 per cent of all node-positive patients).

Because of these results and because it is less invasive and unpleasant for the patient, ultrasonographically guided axillary cytology has been included in the present multicentre sentinel node study. The aim was to determine the sensitivity and specificity of sentinel node biopsy in patients thought to have negative axillary nodes following ultrasonographically guided aspiration cytology. A multicentre study was undertaken to increase recruitment.

Patients and methods

From December 1996 to July 1998, 185 consecutive patients with a clinically axillary node-negative, operable breast carcinoma were treated in the participating hospitals, Zuiderziekenhuis Rotterdam, University Hospital Rotterdam locations Dijkzigt Hospital and Daniel den Hoed Cancer Centre. Mean age of the patients was 54 (range 24–87) years. The pathological size of the breast tumours was less than 10 mm ($T_{1a,b}$) in 36 patients, 11–20 mm (T_{1c}) in 52 patients, 20–50 mm (T_2) in 87 patients and greater than 50 mm (T_3) in ten patients. The location of the tumour was in the lateral upper quadrant in half of the women. Histological examination showed that the tumour was invasive ductal carcinoma in 71 per cent, invasive lobular carcinoma in 17 per cent and other types of invasive breast cancer in 12 per cent. Informed consent was obtained from all patients.

Ultrasonographic evaluation of the axilla was done with an Acuson XP128 (Acuson; Mountain View, California, USA) or Siemens Elegra (Siemens, The Hague, The Netherlands) machine using a 7–10 MHz linear array transducer. The length and width of any identified nodes were measured and the echo pattern was classified as inhomogeneous, homogeneous or node with an echo-rich centre. The first two classifications were considered malignant and the last benign.

If technically possible, ultrasonographically guided aspiration cytology was performed with a 21-G needle. Where two or more nodes were visible in the axilla, only the largest or most suspicious were aspirated up to a maximum of two. The aspiration biopsies were examined after standard Giemsa and Papanicolaou staining. Cytology was classified as benign, malignant or not possible to evaluate. Malignant cytology was based on clusters of epithelial cells with nuclear enlargement, prominent nucleoli and nuclear irregularity.

Patients with cytologically malignant cells in the axillary nodes were spared sentinel node biopsy. In the remainder, identification of the sentinel node was done by peritumoural injection of 30–40 MBq ^{99m}Tc-radiolabelled nanocolloid at least 2·5 h before surgery and intradermal injection of 0·5 ml patent blue dye during operation. The sentinel node was identified with guidance of the RMD-CTC4 probe (Radiation Monitoring Devices, Watertown, Maine, USA) and the blue-stained lymph vessel.

Under general anaesthesia, sentinel node biopsy was performed before definitive surgery, preferably through the planned incision. After sentinel node biopsy a routine complete axillary lymph node dissection was performed. All axillary specimens were processed for histological examination using haematoxylin and eosin staining. The sentinel node was examined in multiple sections (between two and eight, depending on lymph node diameter) and by immunohistochemical staining with a monoclonal cytokeratin antibody against low molecular weight cytokeratin (CAM 5.2).

Results

In all 31 patients with positive cytology from axillary nodes detected by ultrasonographic imaging, subsequent histological examination of axillary clearance specimens confirmed the presence of lymph node metastases (there were no false-positive results). The other 154 patients had either no nodes detected ultrasonographically ($n = 116$) or negative cytology of detected nodes ($n = 38$). In 44 of these 154 patients, metastases were found in the sentinel node on histological analysis with standard haematoxylin and eosin staining. In eight patients a (micro)metastasis was detected using immunohistochemical staining. There were four patients with one or more metastatic nodes in the axillary clearance specimen despite a negative sentinel node (all in the first year).

The overall incidence of metastatic disease in the axilla was 87 (47 per cent) of 185. In 31 (36 per cent) of these 87 patients the lymph node metastases were detected by ultrasonography and cytology (17 per cent of all 185 patients with operable breast cancer). The sensitivity of ultrasonographic detection was low. There was no correlation between the site of the breast tumour and the ultrasonographic detection rate. The more axillary lymph nodes detected by ultrasonography the higher was the percentage of metastases (*Fig. 1*). This suggested that the greatest improvement in the detection of metastases could be obtained by trying to visualize lymph nodes.

Classification of nodes into inhomogeneous or homogeneous as suggesting malignancy seemed to be correct (*Fig. 2*). However, 30 per cent of nodes thought benign, as classified according to an echo-rich centre, were in fact malignant.

As expected, the incidence of lymph node involvement increased with increasing size of the primary breast tumour (*Fig. 3*). Also the rate of detection of lymph nodes by ultrasonography increased with increasing tumour size.

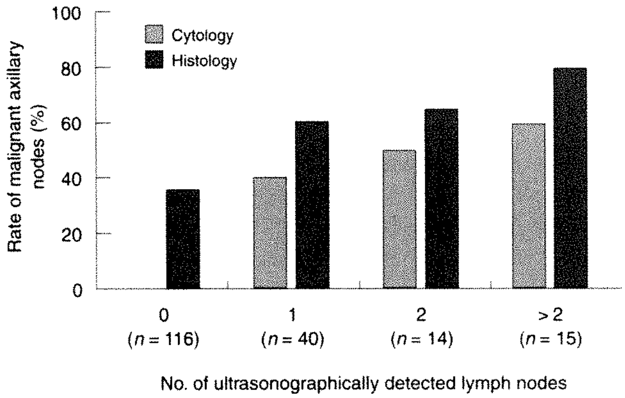

Fig. 1 Relation between the number of lymph nodes detected by ultrasonography and the rate of lymph node malignancy

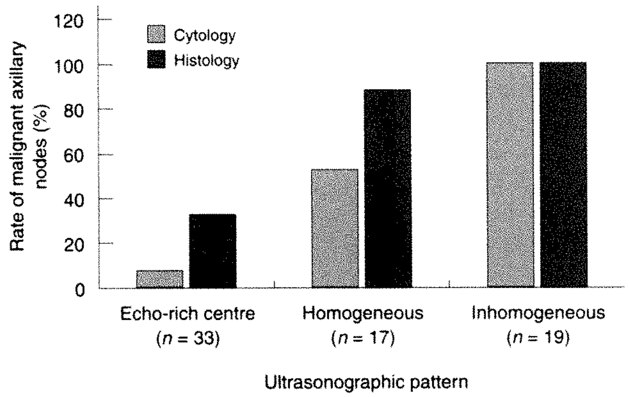

Fig. 2 Relation between ultrasonographic pattern and lymph node malignancy

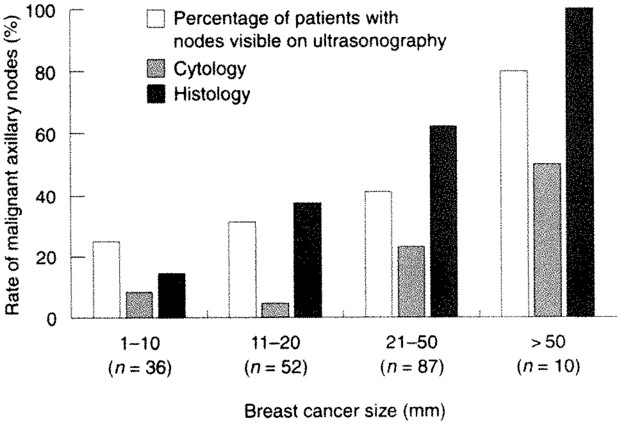

Fig. 3 Relation between tumour diameter and lymph node malignancy

At the start of the study the first hospital had no experience in examining the axilla but was experienced in examining lymph nodes in the neck. The second hospital had 5 years of experience in examining axillary lymph nodes, but after 2 months the most experienced radiologist left. The third hospital had no previous experience. After the initial 50 patients the first hospital had a detection rate of 45 per cent compared with 25 per cent for the second and third hospitals.

Discussion

Removal and histological examination of the axillary lymph nodes is standard for determining whether metastases are present. Besides its role in deciding upon adjuvant treatment, it also prevents axillary node recurrence. The reported incidence of axillary lymph node involvement in breast cancer varies between 30 and 50 per cent. Differences in the number of lymph nodes examined and the techniques of the pathologist account for this variation. If sentinel node biopsy replaced axillary dissection as a staging procedure this should make staging the axilla more accurate because examination of the sentinel node is standard, involving multiple sections and immunohistochemical staining.

The role of ultrasonography of the axilla in breast cancer has been evaluated by a number of investigators. The sensitivity and specificity for axillary involvement is in the range 56–73 per cent and 70–100 per cent, respectively[10–17]. Reports about ultrasonography in combination with cytology are rare[18]. In other tumours, combined ultrasonographic imaging and cytology is common, especially in head and neck cancer[19–21]. Bonnema *et al.*[10] introduced ultrasonography in combination with cytology for the detection of lymph node metastases in patients with breast cancer.

In one of the participating hospitals, ultrasonographically guided cytology of the axilla had been a standard examination for several years, with a sensitivity of 39 per cent and specificity of 100 per cent determined retrospectively. In the present multicentre study, the sensitivity of ultrasonographically guided cytology was 36 per cent. There are some suggestions that could improve the sensitivity of the this technique. First, the place where the sentinel node is most commonly located should carefully be palpated and examined by ultrasonography. This is just behind the pectoralis major muscle at the crossing of the cranial edge of breast tissue and the pectoralis major muscle. Second, cytological examination of a homogeneous or inhomogeneous node could be repeated if the first result is benign. Similarly, the cytological analysis should be repeated in smears with a non-evaluable result. Another advantage of ultrasonography is in the false-negative biopsies of the sentinel node procedure. The commonest cause of a false-negative sentinel node procedure is extensive nodal involvement. If a node is replaced by tumour there is poor uptake of radioactivity. Ultrasonography and cytology is, however, particularly sensitive in patients with extensive axillary node involvement.

Whereas sentinel node biopsy may become standard treatment for patients with small (T_1) breast cancers, the incidence of lymph node metastases in bigger (T_{2-3}) tumours was 58 per cent in the present series. To reduce the number of sentinel node procedures, ultrasonographic examination with cytology is a useful selection procedure. With this examination 17 per cent of the patients will not need sentinel node biopsy since ultrasonographically guided cytology will already have detected metastases and complete axillary node dissection can be performed as a primary procedure.

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In vitro DNA synthesis in freshly separated human breast cancer cells assessed by tritiated thymidine incorporation assay: relationship to the long-term outcome of patients

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Background: Tumour growth rate has a significant effect on the clinical course of various malignancies. The present study was designed to assess whether *in vitro* DNA synthesis in freshly separated breast cancer cells is a useful marker in evaluating growth rates and in predicting the clinical outcome of patients.

Methods: From 1982 to 1992, DNA synthesis was assessed by [^{3}H]thymidine incorporation in 97 samples of primary lesions from 94 patients with breast cancer. The patients were followed for 5–15 years and their outcome was surveyed in January 1998.

Results: The level of DNA synthesis did not correlate with the patients' age, clinical stage or expression of oestrogen receptor. However, it correlated significantly with the histological grade. In 89 patients, whose outcome was reported, the survival rate in the group with a high rate of DNA synthesis ($\log_{10}$c.p.m. 3·0 or more) was significantly lower than that in the low-level group; the 5- and 10-year survival rates were 84 and 74 per cent for the low synthesis group ($n = 46$), and 60 and 46 per cent for the high synthesis group ($n = 43$) respectively. This was also noted in patients with stage 1 or 2 cancers, for whom the 5- and 10-year survival rates were 100 and 90 per cent for the low synthesis group ($n = 25$), and 75 and 70 per cent for the high synthesis group ($n = 35$). Multivariate analysis supported this significant correlation for DNA synthesis in the prognosis of patients after mastectomy. Furthermore, the level of DNA synthesis was significantly higher in 18 patients who died from a recurrence within 3 years after operation than in 56 survivors, and the level of DNA synthesis also correlated significantly with the survival period in the 33 patients who died.

Conclusion: The level of DNA synthesis in breast cancer was variable, and was independent of the clinical stage or oestrogen receptor status. However, a high level of DNA synthesis was a positive indicator of a high risk of recurrence after operation, especially for stage 1 or 2 breast cancer. *In vitro* DNA synthesis may account for some of the clinical characteristics of breast cancers.

Paper accepted 7 June 1999

British Journal of Surgery 1999, 86, 1463–1469

Introduction

Breast cancer is one of the most frequent causes of cancer death in well developed countries. Breast cancers show wide variations in growth rate; the doubling time of breast cancer has been reported as 128 days for primary tumours without nodal involvement and 85 days for primary lesions with nodal involvement[1,2]. Tumour doubling time has been studied clinically for a long time as a prognostic factor[3], and in breast cancer the doubling time of the tumour has been correlated directly with the duration of survival after radical mastectomy[4]. However, doubling time is not always useful in clinical practice, because it is very difficult to assess in primary tumours. Therefore, many researchers have tried to assess the biological characteristics of breast cancers with respect to various clinicopathological factors, such as tumour size, nodal involvement and nuclear or histological grade[5,6].

On the other hand, some researchers have employed various cytomolecular studies, especially flow cytometric analysis or the tritiated thymidine labelling index (TLI), to analyse the growth of breast cancers. DNA ploidy, S-phase fraction and mitotic indices were beneficial in evaluating the malignant potential of breast cancer[7–11]. In addition, some studies have suggested that the proliferative activity assessed by S-phase fraction or DNA ploidy may correlate with the response to chemotherapy[12–14]. Most of these studies were based on the hypothesis that the level of DNA synthesis would reflect the proliferative activity of the tumour cells, and that measurement of proliferative indices may be beneficial in assessing the malignant potential of breast cancer. However, these studies assessed DNA synthesis indirectly in tumour cells and, to the authors' knowledge, no study has evaluated DNA synthesis directly in freshly separated human breast cancer cells or demonstrated a correlation between the malignant potential of tumour cells and the DNA synthesis rate. Furthermore, it is still unclear whether these cytomolecular factors may be as useful as stage classification, histology and histopathological grading as a prognostic factor.

The present study was designed to assess the proliferative ability of freshly separated human breast cancer cells from primary lesions and to identify any correlation between proliferation and clinicopathological factors or the background of the patients. In addition, a multivariate analysis was performed to elucidate whether the DNA synthesis rate may be as useful as stage classification, histology and histopathological grading as a prognostic factor.

Patients and methods

Patients

From 1982 to 1992, samples of primary lesions from breast cancers were sent to the authors' division from four hospitals. DNA synthesis was assayed successfully in 97 samples from 94 patients. There were 93 women; the mean(s.d.) age was 55·9(11·5) years. The tumours were classified according to the Union Internacional Contra la Cancrum tumour node metastasis (TNM) stage classification[15]. After operation, the patients were treated with chemotherapy, endocrine therapy and/or radiotherapy, and followed until 1997. The operations and adjuvant therapies used are summarized in *Table 1*. Usually, patients with stage 1–2 lesions underwent modified radical mastectomy (muscle-preserving mastectomy with axillary dissection), those with stage 3 disease received standard radical mastectomy and stage 4 tumours were treated with palliative mastectomy. For chemotherapy, fluoropyrimidines such as tegafur, uracil and tegafur (UFT), carmofur and 5′-deoxy-5-fluoro uridine were administered orally. Patients with metastasis received intravenous 5-fluorouracil (5-FU), doxorubicin, mitomycin C, cyclophosphamide, etc. Endocrine therapies included tamoxifen, medroxyprogesterone, androgens and oophorectomy. Some patients received radiotherapy. The survival of the patients was surveyed on 1 January 1998, and was reported for 89 of the 94 patients. Follow-up time was 5–15 (median 9·7) years.

Table 1 Operations and adjuvant therapies

	Stage			
	1	2	3	4
No. of patients	35	24	26	8
Operation				
Standard radical mastectomy	1	0	19	6
Modified radical mastectomy	34	24	7	1
Simple mastectomy	0	0	0	1
Chemotherapy				
Oral fluoropyrimidines	30	24	23	5
5-Fluorouracil	5	4	14	5
Mitomycin C	5	4	10	3
Doxorubicin	1	4	14	4
Cyclophosphamide	2	2	7	2
Carboquone	5	3	2	1
Other	1	0	3	0
Endocrine therapy				
Tamoxifen	11	11	11	2
Medroxyprogesterone	0	2	5	0
Androgen	1	2	2	0
Oophorectomy	0	0	1	0
Radiotherapy	0	0	4	0

Stage and therapies were not documented in one of 94 patients

Preparation of tumour cells

This procedure was performed as described previously[16,17]. Briefly, solid tumours were removed surgically, immediately minced into 2–3-mm cubes with scissors in RPMI-1640 (Gibco, Grand Island, New York, USA) medium, and then teased apart with needles. Isolated cells floating in RPMI-1640 were separated from the tissue fragments by passing through a no. 100 stainless steel screen. The same procedure was repeated until the amount of cell suspension collected was no longer significant. The cell suspensions were pooled, and the cells were rinsed three times in Hanks balanced salt solution (HBSS).

The tumour cells were separated from other contaminating blood or matrix components by a three-step Ficoll–Paque (Pharmacia, Uppsala, Sweden) density gradient method. The cell suspension was overlaid on to 50, 80 and 100 per cent Ficoll–Paque in 15-ml tubes, and then centrifuged at 500–600g for 30 min at 8°C. The cells separated in the interfaces were collected and counted. The fractions containing more than 80 per cent tumour cells were used as tumour-rich fractions. The tumour cells were usually separated in the interface between 50 and 80 per cent

Ficoll–Paque, and the infiltrating lymphocytes were usually separated between 80 and 100 per cent Ficoll. If the tumour cell purity was lower than 80 per cent, the same procedure was repeated to purify the tumour cells.

After harvest, the tumour cells were rinsed three times in HBSS and resuspended in culture medium. The medium consisted of RPMI-1640 supplemented with 10 per cent fetal calf serum (Gibco), 1 per cent non-essential amino acids (Gibco), 1 per cent L-glutamine (Gibco), 1 per cent pyruvate (Gibco) and gentamicin 100 µg/ml (Shering, Kenilworth, UK).

In vitro DNA synthesis

DNA synthesis of the tumour cells was assessed by a [^{3}H]thymidine (Amersham, Arlington Heights, Illinois, USA) incorporation assay[16,17]. Tumour cells were cultured in medium at 5×10^4 cells per 0·2 ml per well in 96-well flat-bottom microtitre plates (Corning, Corning, New York, USA) for 60 h. The cells were then labelled with [^{3}H]thymidine (0·5 µCi per 25 µl HBSS) and cultured for a further 12 h (total 72 h). After incubation, the cells were harvested on to glass fibre filters (Labo Science, Tokyo, Japan) by a semiautomatic cell harvester (Titertek; Flow Laboratories, Rickmansworth, UK). Before harvesting the cells, the culture medium in the wells was gently removed with a pipette and 100 µl trypsin–ethylenediamine tetra-acetic acid (EDTA) (0·25 per cent trypsin, EDTA 1 mmol/l; Gibco) was added to the wells to remove the adherent cells from the plastic. The plate was shaken on a plate mixer (Iwaki, Funabashi, Japan) at 37°C for 5–10 min, after which the harvesting procedure was performed. After drying at room temperature, the filters were placed into counting vials (Packard, Meriden, Connecticut, USA) with 3 ml scintillation cocktail (PCS; Amersham), and radioactivity was counted with a liquid scintillation counter (LSC-1000; Aloka, Tokyo, Japan). All experiments were set up in triplicate and mean values were reported. DNA synthesis was expressed as the radioactivity in counts per minute. A logarithmic analysis was applied because the tumour cells usually show logarithmic growth[3] and an increase in the amount of [^{3}H]thymidine incorporation after culture initiation[16,17].

Statistical analysis

The status of all patients after operation was surveyed on 1 January 1998. A χ^2 test was used to compare the background characteristics of the patients; Student's t test and Pearson's correlation coefficient were used to determine statistical significance of observed differences. The cumulative survival rates were calculated by the Kaplan–Meier method. To compare the survival curves, a Cox–Mantel test was used. A multivariate analysis of the maximum likelihood estimates with Cox's proportional hazard model was used to obtain the conditional risk of death from breast cancer. All analyses were performed using the SAS computer software (SAS Institute, Cary, North Carolina, USA), and $P < 0{\cdot}05$ was considered to be significant.

Results

DNA synthesis in primary lesions and clinicopathological background

The rate of DNA synthesis was assessed by measuring the [^{3}H]thymidine incorporation into the cells. The level of DNA synthesis did not correlate with the patients' age, clinical stage or expression of oestrogen receptor. However, it correlated significantly with the histological grade in a Pearson correlational analysis; the rate was highest in medullary carcinoma, followed by invasive ductal carcinoma, invasive lobular carcinoma and non-invasive intraductal carcinoma in descending order. The level of DNA synthesis in non-invasive ductal carcinoma was significantly lower than that in medullary carcinoma (*Table 2*). Three patients had multiple primary lesions: two had bilateral breast cancers and one had two lesions in a single breast. The DNA synthesis levels in the multiple primary lesions in the same patients were almost equal (data not shown).

Correlation between rate of DNA synthesis and outcome after operation

The level of DNA synthesis was assayed from 1982 to 1992, then patients were followed until 1997; outcome was known for 89 of 94 patients. During the median follow-up period of 9·7 years, 33 patients died from a recurrence of the breast cancer, whereas 56 are alive and disease free. A cut-off level of DNA synthesis for the most significant effect on the prognosis was obtained by comparing the survival rates above and below different cut-off values in a stepwise manner. When $\log_{10}$c.p.m. 3·0 was used as the cut-off point, the most significant difference in survival curves was demonstrated between a high DNA synthesis group ($\log_{10}$ c.p.m. 3·0 or more) and a low synthesis group. The 5- and 10-year survival rates were 84 and 74 per cent for the low synthesis group ($n = 46$), and 60 and 46 per cent for the high synthesis group ($n = 43$) respectively (*Fig. 1*). This difference in survival between the high and low synthesis groups was also noted in the subset of patients with stage 1 or 2 breast cancers; the 5- and 10-year survival rates were 100 and 90 per cent for the low synthesis group ($n = 25$), and 75 and 70 per cent for the high synthesis group ($n = 35$). However,

Table 2 DNA synthesis related to pathological characteristics of primary lesions

Variable	Rate of DNA synthesis ($\log_{10}$c.p.m.)*	*P*	*r*
Overall	3·08(0·48)		
Age (years)		n.s.†	
≤50 (*n*=32)	3·18(0·61)		
>50 (*n*=62)	3·04(0·40)		
Stage (pTNM)		n.s.†	
1 (*n*=36)	3·06(0·48)		
2 (*n*=24)	2·94(0·39)		
3 (*n*=26)	3·23(0·57)		
4 (*n*=8)	3·12(0·32)		
Histology (WHO)			
Non-invasive intraductal carcinoma (*n*=4)	2·70(0·23)	<0·01‡§	
Invasive ductal carcinoma (*n*=78)	3·08(0·49)		
Medullary carcinoma (*n*=6)	3·42(0·42)		
Invasive lobular carcinoma (*n*=3)	2·94(0·28)		
Histological grade		0·033†	0·226
1 (*n*=17)	2·90(0·32)		
2 (*n*=38)	3·09(0·46)		
3 or 4 (*n*=25)	3·14(0·60)		
Oestrogen receptor status		n.s.‡	
Positive (*n*=45)	3·06(0·53)		
Negative (*n*=18)	3·09(0·58)		

*Values are mean(s.d.). Multiple lesions were included. pTNM, pathological tumour node metastasis; WHO, World Health Organization; n.s., not significant. †Pearson's correlation coefficient between variables and rate of DNA synthesis; ‡Student's *t* test; §*versus* medullary carcinoma

Table 3 Comparison of DNA synthesis rates in primary lesions between survivors and non-survivors

	n	Rate of DNA synthesis ($\log_{10}$c.p.m.)*
Living	56	3·04(0·49)†
Deceased	33	3·18(0·47)
Within 3 years after operation	18	3·36(0·52)
After 3 years	15	2·96(0·30)‡

*Values are mean(s.d.). †$P < 0·05$, ‡$P < 0·02$ *versus* patients who died within 3 years after operation

there was no difference in survival in patients with stage 3 or 4 breast cancers, in whom the 5- and 10-year survival rates were 36 and 27 per cent for the low synthesis group (*n* = 11) and 35 and 18 per cent for the high synthesis group (*n* = 17).

Further analysis also demonstrated that the level of DNA synthesis in patients who died within 3 years after surgery was significantly higher than that in patients who died more than 3 years after operation or who survived. However, there was no difference in the level of DNA synthesis in the primary lesions between the survivors and non-survivors (*Table 3*). This was also demonstrated in an analysis using the correlation efficiency, in which a significant but inverse correlation was noted between the survival period of non-survivors and the level of DNA synthesis in the primary lesion ($r = -0·3992$, $P < 0·05$) (*Fig. 2*).

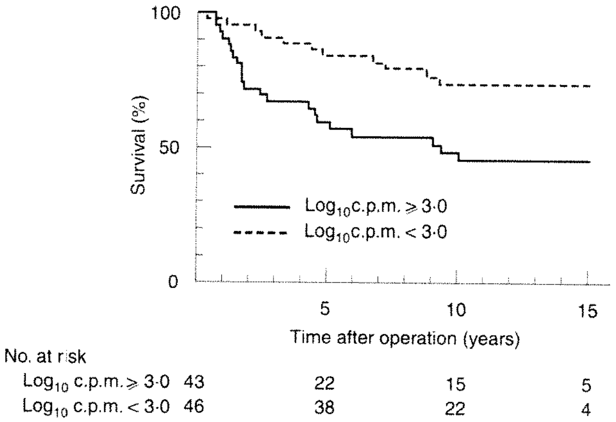

Fig. 1 Rate of DNA synthesis in primary lesions and survival after operation. The survival curves for the high DNA synthesis group ($\log_{10}$c.p.m. 3·0 or more) and low synthesis group were significantly different ($P < 0·01$, Cox–Mantel test)

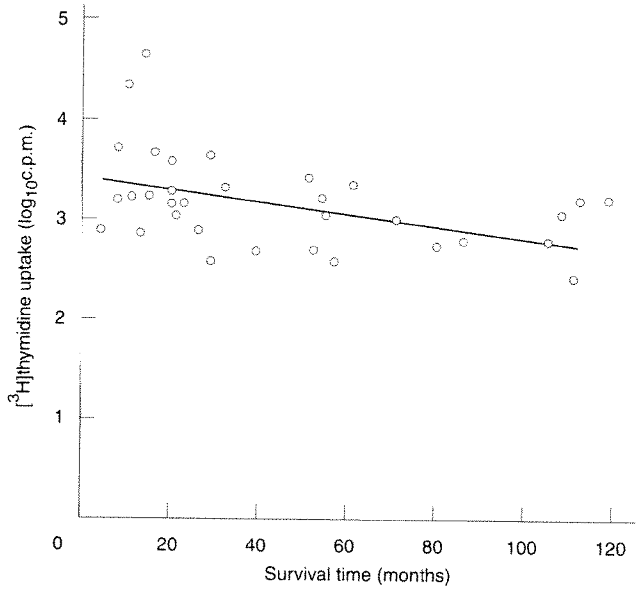

Fig. 2 Correlation between rate of DNA synthesis in primary lesions and survival time in patients who died from recurrence of breast cancer. A significant but inverse correlation was noted ($r = -0·3992$, $P < 0·05$)

Table 4 Correlation between various clinicopathological factors and the rate of DNA synthesis and prognosis of patients with resectable breast cancer

	Parameter estimate*	Conditional risk ratio†	*P*§
Age (years)	−0·06(0·03)	0·94 (0·90–0·99)	0·02
pT‡	−0·38(0·40)	0·68 (0·31–1·49)	0·34
pN‡	2·37(0·52)	10·73 (3·88–29·69)	0·0001
M‡	1·26(1·22)	3·51 (0·32–38·38)	0·30
Histological grade	0·09(0·10)	1·09 (0·90–1·32)	0·37
Oestrogen receptor	−0·78(0·56)	0·46 (0·15–1·37)	0·16
DNA synthesis	1·13(0·53)	3·10 (1·10–8·76)	0·03
Chemotherapy	−3·96(1·16)	0·02 (0·00–0·18)	0·0006
Endocrine therapy	−0·83(0·59)	0·44 (0·14–1·38)	0·16
Radiotherapy	0·01(0·77)	1·01 (0·22–4·54)	0·99

Values in parentheses are *standard errors and †95 per cent confidence intervals. Multivariate analysis was by Cox's proportional hazard risk model, with month as the dependent variable and death from recurrence of breast cancer as the censoring variable. This analysis excluded patients whose oestrogen receptor status was not studied. ‡Pathological tumour node metastasis (pTNM) classification. §χ^2 test

Multivariate analysis

The analyses used to evaluate the survival curves did not include differences in the patients' backgrounds, and therefore a multivariate analysis of the maximum likelihood estimates using Cox's proportional hazard risk model was performed to determine the significant risk factors for death from breast cancer after operation (*Table 4*). The multivariate analysis demonstrated that age, nodal involvement, chemotherapy and the DNA synthesis level showed significant risk ratios, but that primary tumour stage, distant metastasis, histopathological grade, oestrogen receptor status and various other therapies were not significant as risk factors.

Discussion

In the present study, the level of DNA synthesis was evaluated on a logarithmic scale because the growth of malignant tumour is typically logarithmic. The level of DNA synthesis in the primary lesion did not correlate with the patients' age, clinical stage or expression of oestrogen receptor, but it did correlate significantly with the histopathological grade of the tumour. However, this does not necessarily mean that the level of DNA synthesis does not reflect the growth of the tumour, because the histological grade has also been reported to be an important prognostic factor, and can improve the prediction of outcome when used in conjunction with the stage of the breast cancer[18,19]. Furthermore, large tumours do not always show rapid growth and sometimes have a long history after first detection, which suggests that tumour size may simply represent tumour growth in the past. On the other hand, multiple primary lesions showed almost the same level of DNA synthesis in individual patients, which suggests that they might derive from the same clone. However, it was not possible to distinguish whether multiple primary lesions arose from multicentric generation or intraductal skip metastasis in the breast.

A high level of DNA synthesis in the primary lesion was significantly associated with a lower survival rate after operation (*Fig. 1*), and the level of DNA synthesis in the primary lesion was found to be a significant prognostic factor in multivariate analysis (*Table 4*). Furthermore, the results shown in *Table 3* suggest the possibility that the patients with breast cancer may be classified into two distinct groups, one with a high DNA synthesis rate and a very low survival rate, and the other with a low DNA synthesis rate in which survival is not related to DNA synthesis. A poor prognosis for patients with a high level of DNA synthesis was noted only in patients with stage 1 or 2 cancer; there were no differences in survival between the high and low DNA synthesis groups in patients with stage 3 or 4 disease. Furthermore, nodal involvement was found to be a significant factor for the prognosis of patients with resectable breast cancer in multivariate analysis. This suggests that nodal involvement is the crucial factor for the prognosis of patients with advanced cancer (stage 3 or 4). Thus, measurement of the DNA synthesis level in involved nodes may be more useful in predicting the prognosis of patients with advanced cancer than evaluating the primary lesion. This is supported by the observation that the T factor was not significant in multivariate analysis. Previous reports have also demonstrated that tumour size is most influential in node-negative patients[5]. Taken together, these results suggest that cytomolecular or immunohistochemical studies used to evaluate the proliferative activity of tumour cells should be performed in involved nodes or other key lesions to determine the prognosis.

In the present multivariate analysis, chemotherapy was a significant variable for better outcome. Many reports on the benefits of adjuvant chemotherapy have been contradictory. Different regimens and backgrounds of the patients may be possible reasons for the conflicting results. Chemotherapy, especially adjuvant chemotherapy, regimens for breast cancer in Japan differ from those in European countries and the USA. In Japan, oral fluoropyrimidines have been popular[20–22]. A representative agent of this group, UFT, showed an effect comparable to that of 5-FU; a regimen of oral UFT combined with leucovorin was as potent as intravenous 5-FU plus leucovorin in treatment of colorectal cancer[23,24]. This may be one of the reasons why chemotherapy was a significant variable for better survival in the present study. On the other hand, endocrine therapy was not a significant variable. In the present study tamoxifen was the main form of endocrine therapy. However, when the study started, tamoxifen was less popular and it was administered to premenopausal patients as well as postmenopausal patients, sometimes without evaluation of oestrogen receptor status. This may be one of the reasons why endocrine therapy was not a significant variable in multivariate analysis.

For the evaluation of the DNA content and proliferative activity in breast cancers, two representative methods, flow cytometry and TLI, have been used over the past two decades. DNA content and cell proliferation, which were measured by flow cytometry from paraffin-embedded specimens, have been shown to be important and independent prognostic factors for various cancers in predicting recurrence and prognosis[7–11,14]. Flow cytometric analysis reflects the static condition of the cellular DNA, like ploidy pattern and cell cycle analyses, and does not show the actual rate of DNA synthesis. TLI has also been used to determine the proliferative activity of breast cancers; this assay system can measure the proliferative activity of tumour cells more directly than flow cytometric analysis. TLI was reported to be a useful predictor of patient outcome[11,25]. However, TLI has several disadvantages in that it uses radioisotopes and requires fresh specimens, the technique is difficult and the use of minced specimens for the assay makes it difficult to compare the results between patients. The present assay, which measures the level of DNA synthesis by [^{3}H]thymidine incorporation, has an advantage in that it can evaluate DNA synthesis more directly and more objectively than flow cytometric analysis. This assay has the same underlying basic concept as TLI; however, it can evaluate DNA synthesis more accurately and can be standardized more easily, because it uses the same number of tumour cells, whereas the number of cells contained in the minced specimens is unclear in the TLI assay. However, this assay system has several problems in common with TLI in that it uses a radioisotope, which restricts its broad application to clinical use. The assay also needs fresh specimens, and should start within 24 h after the resection in order to obtain enough viable tumour cells. It also takes several (usually 4–5) days to obtain the results.

On the other hand, measuring the level of DNA synthesis may be beneficial in selecting patients who need more intensive adjuvant therapy, because tumour cells with a high level of DNA synthesis are more sensitive to anticancer drugs[16,17]. The application of chemotherapy to patients whose tumours show a high level of DNA synthesis may contribute to reduced or delayed recurrence, and may improve the prognosis of patients with a high risk for recurrence. Accordingly, these cytomolecular studies could modify the stage classification, especially for stage 1 or 2 disease; for example, stage 2s would mean that the patient has a stage 2 cancer with a slow growth rate, and stage 2r would mean a stage 2 cancer with a rapid growth rate.

In conclusion, measuring the level of DNA synthesis in tumour cells is useful in assessing the proliferative activity and biological characteristics of breast cancers, but a more simple assay system should be introduced.

Acknowledgements

The authors thank Professor Norio Kurihara for advice on the experiments using radioisotopes, and Ms Hiroko Yagi and Ms Hiroko Higashikawa for excellent technical assistance.

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Short note

Endoscopic technique for the localization of intraduct papillomas

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Presented as a poster to the XVIIth National Congress of the Spanish Senology Society, Vigo, Spain, October 1998
Paper accepted 26 June 1999

Introduction

Intraduct papillomas are situated in the main lactiferous ducts[1]. Intraoperative localization for removal is not always easy. This paper describes an intraoperative method for localizing single intraduct papillomas using lactiferous duct endoscopy.

Surgical technique

The operation is done under general anaesthesia using a 4·5-Fr Wolf infant endoscope with an 0·8-mm working channel, 4-, 5- and 6-Fr dilators, and a 0·035-inch metallic guidewire. Two silk 2/0 sutures are inserted at the base of the nipple to start the operation. With the aid of two securing forceps, the trajectory of the lactiferous ducts can then be adjusted to ease insertion of the endoscope. The secreting duct is located and the guidewire inserted through the lactiferous duct. Progressively thicker dilators are then inserted over the guidewire until the endoscope can be inserted, usually after insertion of the 6-Fr dilator.

Endoscopy of the lactiferous duct is then performed. Once the papilloma is located, a guidewire is passed through the working channel of the endoscope, checking by means of direct and endoscopic vision that it remains in the papilloma-containing lactiferous duct (*Fig. 1*). The endoscope is then gently removed.

A periareolar incision is then made as close as possible to the lactiferous duct containing the guidewire. The retroareolar tissue is dissected until the lactiferous duct is reached immediately beneath the skin of the nipple. The duct is easily identifiable because of the guidewire. The duct is dissected until the end of the guidewire has been passed (*Fig. 2*); the lactiferous duct is then sectioned and removed.

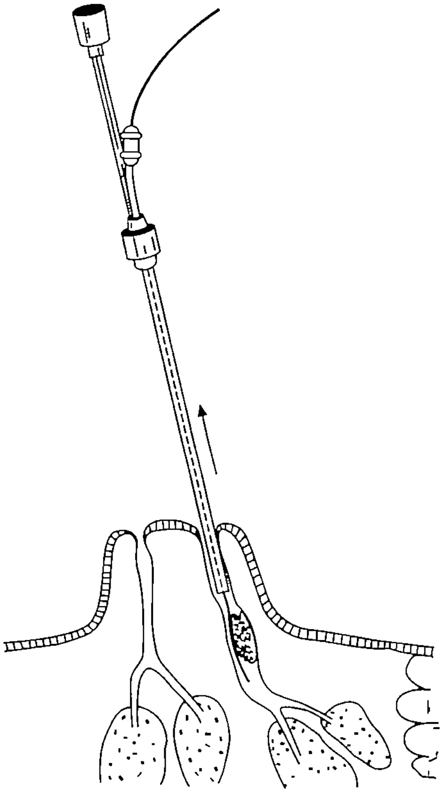

Fig. 1 Insertion of the guidewire through the working channel of the endoscope followed by removal of the endoscope

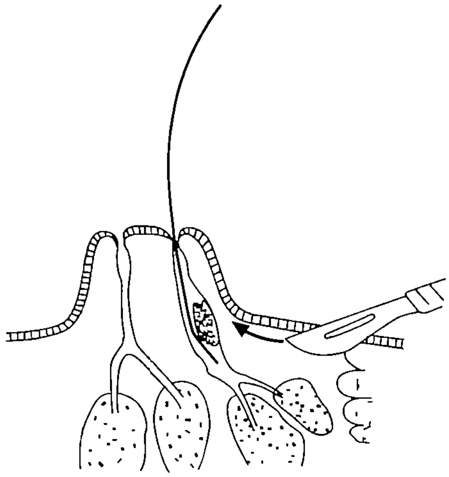

Fig. 2 Guidewire inside the papilloma-containing lactiferous duct, which can be located easily for excision

The duct is opened lengthwise and the papilloma marked. The retroareolar area is then repaired.

Discussion

Endoscopy of the lactiferous duct is a technique that has been used for various purposes since 1991[2–4]. Until now, intraoperative localization of intraduct papillomas has been carried out by inserting different materials through the lactiferous duct, such as catheters, stains (e.g. methylene blue) and polypropylene monofilament thread[5].

In contrast to other procedures, the technique described in this study, as well as confirming the preoperative diagnosis, allows the guidewire to be inserted and placed within the intraductal papilloma-containing duct. This guarantees that the duct papilloma is removed.

This procedure has been used in eight consecutive patients with an intraduct papilloma diagnosed by cytology or ductography (one bilateral). In seven procedures the papilloma was located and excised; this was confirmed by incising the lactiferous duct. In two procedures a papilloma could not be identified. Macrodochectomy was undertaken in these patients and histological examination confirmed a diagnosis of duct ectasia. There were no complications and no recurrence up to a mean follow-up of 16 months.

In the future, with a little more experience and the right instruments, the removal of an intraduct papilloma may be possible with endoscopic methods.

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24-h pH monitoring is necessary to assess acid reflux suppression in patients with Barrett's oesophagus undergoing treatment with proton pump inhibitors

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Background: Control of acid reflux is the main objective of treatment for Barrett's oesophagus. However, as these patients have a reduced sensitivity to acid reflux, disappearance of symptoms may not correlate with efficient control of acid reflux. The aim of this study was to determine in a group of patients with Barrett's oesophagus whether treatment with proton pump inhibitors suppressed pathological acid reflux once the symptoms of reflux had been controlled and the associated inflammatory lesions cured.

Methods: Eighteen consecutive patients with Barrett's oesophagus were studied, all of whom presented with heartburn. Twenty-four-hour oesophageal pH monitoring before treatment showed pathological acid reflux in all cases: median percentage of total time with pH less than 4, 22 (range 8–52) per cent. All patients received proton pump inhibitors (dose 20–60 mg/day) until symptoms were controlled.

Results: While on therapy, pH was reduced (median percentage of total time with pH less than 4, 3 *versus* 22 per cent; $P < 0.001$). However, three patients had persistent pathological rates of acid reflux.

Conclusion: Disappearance of symptoms is not a good indicator of control of pathological acid reflux in patients with Barrett's oesophagus. Twenty-four-hour pH monitoring should be performed for proper adjustment of the dose of medication.

Paper accepted 7 July 1999

British Journal of Surgery 1999, **86**, 1472–1474

Introduction

One of the therapeutic options in patients with Barrett's oesophagus is conservative treatment with proton pump inhibitors (PPIs), which in most cases results in control of the symptoms[1]. However, these patients often present with less mucosal sensitivity to the presence of acid than patients with oesophagitis but without Barrett's oesophagus[2,3]. This raises the question of whether the disappearance of symptoms is a good indicator of control of acid gastro-oesophageal reflux, which constitutes one of the main objectives in the management in order to prevent the benign and malignant complications of Barrett's oesophagus. The aim of this study was to determine, using 24-h pH monitoring, whether in a group of patients with Barrett's oesophagus undergoing treatment with PPIs pathological acid reflux was suppressed once the symptoms of reflux disease had been brought under control and the associated inflammatory lesions cured.

Patients and methods

Eighteen consecutive patients with a diagnosis of Barrett's oesophagus were studied. Twelve patients were male and six female, with a median age of 55·5 (range 12–78) years. All patients presented with symptoms of gastro-oesophageal reflux disease (*Table 1*). Barrett's oesophagus was diagnosed when endoscopy revealed intestinal columnar epithelium lining the distal oesophagus, confirmed histologically in all cases. Eleven patients showed inflammatory lesions associated with the metaplasia, which were categorized according to Savary–Miller's classification[4]: grade II oesophagitis, one case; grade III, two cases; and grade IV, the remaining eight, due to the presence of stenosis and/or ulceration. The median length of the metaplastic segment was 4·4 (range 3–10) cm.

Before medical treatment was started, 24-h pH monitoring was performed in all patients with a portable pH measuring device (Synectics, Stockholm, Sweden). The

Table 1 Symptoms in 18 patients with gastro-oesophageal reflux disease

	No. of patients
Heartburn	18
Regurgitation	10
Dysphagia	5
Chest pain	5
Haemorrhage	3
Epigastric pain	2

equipment consisted of a monocrystal antimony pH electrode, a silver–silver chloride reference electrode and a solid-state box. After calibration at pH 7 and 1, the pH electrode was passed through the nose and positioned in the oesophagus 5 cm above the lower oesophageal sphincter, previously located by manometry. The reference electrode was placed on the chest and the memory box was worn in a waist belt. Patients were instructed to lead as normal a life as possible and to take normal meals, with the exception of acid food and beverages. After the monitoring period, the data were analysed with a computer program (Esophogram; Gastrosoft, Irving, Texas, USA) on a personal computer. Following the methodology of Johnson and DeMeester[5], the cumulative exposure of the oesophagus to acid was expressed as the percentage of time for which the pH was less than 4 during the study period, and defined as abnormal when it exceeded 4·5 per cent. All patients demonstrated pathological rates of acid gastro-oesophageal reflux, with a median percentage of time with pH less than 4 of 22 (range 8–52) per cent and a median score of 91 (range 21–191).

Medical treatment was implemented in all cases with omeprazole at doses of 20–60 mg/day until symptoms were brought completely under control. Annual endoscopic assessment was carried out in all patients by the same endoscopist. For the present study the patients underwent further endoscopy and 24-h pH monitoring while on therapy for a median of 24 months (range from 2 months to 7 years). Patients in whom complete suppression of symptoms was not achieved despite high doses of omeprazole (60 mg/day) were excluded from the study ($n = 2$). Also excluded were patients in whom there was doubt as to whether they had followed the therapeutic protocol strictly ($n = 1$).

The mean(s.d.), median and range were calculated for all data. The Wilcoxon rank sum test for paired data was used for comparative results.

Results

All patients were symptom-free after PPI therapy. Endoscopy showed that associated inflammatory lesions had been cured in all cases. The pH study revealed a significant decrease in pathological rates of acid gastro-oesophageal reflux (*Fig. 1*). The median percentage of total time with pH less than 4 fell from 22 to 3 per cent, and the DeMeester score fell from a median of 91 to 10 ($P < 0{\cdot}001$). However, three patients showed pathological rates of acid reflux despite being completely asymptomatic, with a percentage time with pH less than 4 of 6, 11 and 15 per cent (*Fig. 1*) and a DeMeester score of 17, 43 and 53. These three patients received a dose of omeprazole of 20, 20 and 40 mg/day for a median follow-up period of 6 months.

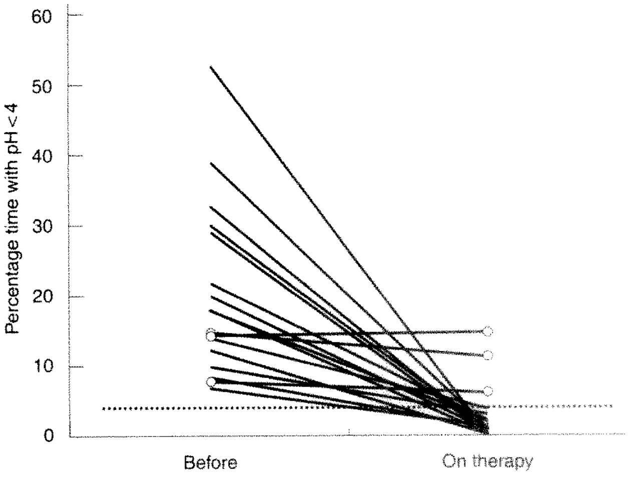

Fig. 1 Percentage of total time with pH less than 4 before and while on therapy. The dotted line denotes the upper range of normal. Note that three patients (○) had abnormal rates of acid reflux despite being asymptomatic

Discussion

The main objective of therapy in Barrett's oesophagus is to eliminate gastro-oesophageal reflux in the hope that reducing the harmful action of the gastric contents on the oesophageal mucosa leads to fewer complications, either benign or malignant, of the Barrett's metaplasia. However, treatment is still controversial. For some authors[6], the therapy of choice is medical treatment, reserving surgery for when this fails. Conversely, others[7,8] advocate surgical treatment from the outset because, although PPIs may bring the symptoms under control, they must be maintained for life, so that medical therapy is expensive and high doses may be required to achieve the therapeutic objective. Furthermore, medical treatment does not modify the mechanical defect of the lower oesophageal sphincter, nor does it improve the motor activity of the oesophageal body, which means it does not suppress the harmful action of biliopancreatic reflux that may be involved in the genesis of this disease and/or its complications.

This study, like a previous study[9], shows that even if patients become asymptomatic with high doses of omeprazole, perhaps with considerable improvement of the endoscopic lesions, the oesophagus is still exposed to the irritating action of acid; complete suppression of acid reflux is not always achieved, as highlighted in three of the present patients. Persistence of acid reflux in these patients may facilitate progression of the sequence from metaplasia to dysplasia and then to adenocarcinoma.

The reason why PPIs do not, in some cases, bring acid secretion under control is unclear. According to some authors[9,10] the most likely causes are gastric acid hypersecretion, inadequate absorption of drugs or excessive drug metabolism, although none of these hypotheses has been verified.

In the authors' opinion, and as reported previously[7,8], medical treatment gives poorer results than surgery, from both an endoscopic and a histological point of view. This is due, perhaps, to inadequate acid suppression or failure to control reflux of duodenal contents. However, real doubt still exists regarding the most appropriate method of management in patients with Barrett's oesophagus, and much further work is required to assess this question. In any case, it is clear that, if medical treatment is opted for, disappearance of symptoms is not a good indicator of whether gastro-oesophageal reflux is controlled. For this reason, the authors consider it necessary to perform pH-metric control and to adjust the dose of PPIs until the pH study indicates the absence of pathological acid reflux. The pH-metric control of reflux may occasionally require high doses of omeprazole (60 mg/day), which is why surgery may be the treatment of choice as a first therapeutic option in these patients, especially if they are young and are not at high operative risk.

Acknowledgements

This work was supported by a grant from the Fondo de Investigaciones Sanitarias de la Seguridad Social, Madrid, Spain.

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Role of superficial venous surgery in the treatment of venous ulceration

Letter 1

Sir

We believe this article (*Br J Surg* 1999; **86**; 755–9) to be an excellent observational study covering an extremely important yet relatively untouched area of venous ulcer management.

We run a similar leg ulcer assessment clinic offering superficial venous surgery to patients with superficial venous reflux alone. We have also identified a subgroup of 15–20 per cent of patients within this group who, despite surgery, fail to heal by 12 months. Prediction of patients who fail to respond to surgery would save unnecessary surgery. The predictive role of digital plethysmography in assessing changes in calf-muscle pump function before and after tourniquet occlusion of an incompetent superficial venous system has some limitations[1]. The synchronous use of a duplex probe to verify superficial vein occlusion in the presence of deep vein patency may provide a useful modification of this technique.

The authors imply that skin grafting larger ulcers would condemn patients to bed for up to 10 days. We believe that pinch skin grafting venous ulcers greater than 3 cm in diameter speeds epithelial regrowth while maintaining patient mobility. A trained specialist nurse carries out this procedure in the clinic under local anaesthesia, with the leg then compressed in four-layer bandaging.

As all dependent legs swell even in the absence of venous reflux we feel that compression and elevation is beneficial to healing even after surgical correction of the superficial venous reflux. This may be evident in 'venous' ulcerated legs with normal venous duplex scans, which respond well to compression, with 75 per cent healing at 24 weeks[2].

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Letter 2

Sir

Bello and colleagues have demonstrated the efficacy of surgery alone for leg ulceration due to chronic venous disease. There are few reports of the long-term results of surgical treatment[1].

We examined the vascular laboratory records at the Middlesex Hospital to locate patients with venous ulceration attributable to superficial venous insufficiency (SVI). Of 88 such patients, we were able to contact 52 and telephone interviews or questionnaires were used to assess the outcome (*Table 1*).

Table 1 Rate of initial healing and persistence of ulcers at the time of surgery in patients with ulceration due to superficial venous disease only

	Surgery ($n=41$)	Conservative ($n=11$)	All ($n=52$)	P
Healed ulcers	37	6	43	0·01*
Recurrence	9	2	11	0·32*
Stockings	35	7	42	0·09*
Persisting symptoms	19	6	25	>0·05†

There was a higher recurrence rate in the group without surgery. Mean follow-up period since initial duplex examination was 52 (range 12–108) months. Probability statistics are those for differences between surgical and conservative groups. *Fisher's exact test; †χ^2 test

Saphenofemoral junction ligation and stripping of the long saphenous vein was the commonest procedure (over 70 per cent). Perforator incompetence was reported in only 4 per cent. The mean follow-up period was 52 (range 12–108) months. More than 40 per cent had to use stockings permanently for troublesome symptoms.

Surgical treatment showed higher initial healing rates compared with conservative treatment, but the recurrence rates and the number of ulcers at the time of the study were similar. Other studies have shown similar results[2].

Despite high initial rates of ulcer healing obtainable with surgery for duplex-confirmed SVI, recurrence rates may be substantial in the long term. This suggests that either the altered venous haemodynamics are not corrected at initial operation and/or these patients develop an irreversible microangiopathy of the skin. Every effort should be made to make varicose vein surgery anatomically and haemodynamically precise[3]. Further studies into the microcirculatory aspects of the disease are equally important. Until definite answers are found, compression therapy will continue to have an important role in many of these patients.

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Authors' reply

Sir

We thank Mr Barwell and colleagues and Messrs Shoab and Coleridge Smith for their letters concerning our paper. We agree with Barwell *et al.* that it would indeed be useful to be able to identify patients with isolated superficial venous insufficiency whose ulcers will not heal after surgery. Presently, however, there is no method of doing this. We did not use pinch skin grafting for two reasons. First, it would not have been possible to determine the specific role of surgery if we had used pinch skin grafting and, second, there is no evidence of benefit from its use. Similarly, we did not use postoperative compression bandaging because it would not then have been possible to determine the specific role of superficial venous surgery. It is interesting to note that our 24-week healing rate after superficial venous surgery without compression bandaging (60 per cent) is little different to that achieved by Mr Barwell's group (69 per cent[1]) with compression bandaging.

We note that Messrs Shoab and Coleridge Smith found a 22 per cent ulcer recurrence rate in patients with venous ulceration and superficial venous ulceration who have undergone surgery. We have been following our patients carefully and at 2 years the recurrence rate is 4 per cent. It is interesting to note that Ghauri *et al.*[1] found a recurrence rate of 9 per cent at 1 year. It is difficult to be sure in the absence of detailed methodology why Mr Shoab's group has a higher recurrence rate and we look forward to being able to view a more detailed report in due course.

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Anomalous pancreaticobiliary junction without choledochal cyst

Sir

Sugiyama and Atomi concluded that prophylactic cholecystectomy alone was sufficient to treat anomalous pancreaticobiliary junction (APBJ) associated with a non-dilated common bile duct (CBD), as evidenced by the absence of bile duct cancer on follow-up *(Br J Surg* 1998; **85**: 911–16). In response, Khan and Manas argued for concomitant excision of the CBD *(Br J Surg* 1999; **86**: 843–4), citing another 'longer' series documenting no malignancy after total excision of the extrahepatic biliary tree. This series had a mean follow-up not much longer than that of Sugiyama and Atomi (6·0 *versus* 4·7 years) and a smaller number of patients (13 *versus* 18 patients). The series included only type IV choledochal cysts. They hypothesized that prevention of reflux of pancreatic enzymes into the biliary tree by the hepaticojejunostomy could 'halt ongoing carcinogenesis'.

In fact, there exist in the literature several reports of malignancy following CBD excision for APBJ; the tumour arose either in the intrahepatic bile duct[1–4], or extrahepatically at or just above the hepaticojejunal anastomosis[5–7]. Recently, we diagnosed cholangiocarcinoma in a 32-year-old woman who, 13 years previously, had undergone CBD excision and hepaticojejunostomy[8].

In addition to the calculated cancer risk alluded to by the authors we would point out more 'direct' evidence favouring CBD excision despite absence of dilatation: the CBD above the APBJ has consistently shown extensive ulceration, fibrosis, inflammation and even mucosal metaplasia and dysphasia, features that may lead to progressive weakening, dilatation and finally malignant degeneration[8–11].

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Trauma centres in the USA – past and present
Trauma centres: a British perspective

Letter 1

Sir

The two leading articles by Champion (*Br J Surg* 1999; **86**: 721–2) and Earlam (*Br J Surg* 1999; **86**: 723–4) on trauma centres are a timely reminder of how the UK is lagging behind in the organized management of the major cause of death and disability in children and young adults.

Training in acute trauma management has undoubtedly progressed over the past decade, largely due to the success of the advanced trauma life support courses. To use these skills effectively, two other ingredients are required: the appropriate facilities and organized management systems between and within these facilities, including management protocols and communication systems.

The organization of trauma management, whether based on the American 'trauma centre' model or the 'inclusive' hub-and-spoke model, should take into account local needs and available resources, but must be ready to break away from traditional practices and look to the future. As Earlam points out, many of the obstacles to developing multidisciplinary trauma centres have historical roots, but contemporary developments often perpetuate these deficiencies. Structured guidance within a national framework, linked to government support, is essential. Such guidance should embrace a comprehensive trauma system, including facilities and resources, the relationship between specialist centres and district hospitals, the organization and delivery of prehospital, emergency and definitive hospital care, rehabilitation and accident prevention.

Surgeons of all disciplines have a responsibility to contribute to this, both as individuals and through relevant organizations. The surgical Royal Colleges in particular have a lead role to play. The issue is too important and too costly, both in human terms and economically, to be left to 'local enthusiasm' and 'luck'[1].

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1 Earlam R. Trauma centres: a British perspective. *Br J Surg* 1999; **86**· 723–4.

Letter 2

Sir

Champion's statement (*Br J Surg* 1999; **86**: 721–2) that the required level of skill in trauma care is only achievable through high-volume repetition highlights the dilemma facing rural district general hospitals (DGHs). Studies in the USA have shown remarkable improvement in survival when seriously injured patients bypass the nearest local hospital to reach a regional trauma centre[1,2].

In the UK the argument for or against regionalizing trauma care was not supported by the North Staffordshire study[3]. An assessment of the performance of rural DGHs that deal infrequently with those with severe injury has never been made. A retrospective study showed that a general surgeon in a rural DGH dealt with a severely injured patient once or twice a year and this may have led to suboptimal management[4].

In the absence of regional trauma centres rural DGHs will continue to receive seriously injured patients. As the argument about regionalizing trauma care has not been resolved, the emphasis at this stage should be on upgrading the existing system. Such upgrade can be achieved by establishing local multidisciplinary trauma committees to initiate: (1) developing prehospital triage systems with improved specificity to ensure involvement of senior surgical staff at an early stage in all life-threatening injuries; (2) establishing a rapid-response trauma team with clear guidelines on how it should be activated; (3) increasing level of consultant involvement; (4) editing and regularly updating a booklet containing all agreed treatment protocols and guidelines; and (5) organizing a continuous programme of trauma training, teaching and audit to ensure that efficient modern trauma management is provided.

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The sportman's groin

Sir

I was interested in the leading article on sportsman's groin (*Br J Surg* 1999; **86**: 849–50). I must confess to having originally been a sceptic about the existence of this syndrome, but am a recent convert to the concept. The problem is that, as the authors indicate, there are a wide variety of pathologies. I am not sure that it helps to include the nerve entrapment syndromes and osteitis pubis. Even when these are excluded, exploration of the inguinal canal, with careful reconstitution of the normal anatomy, will not invariably be successful, though a careful attempt at accurate diagnosis should result in fewer disappointed sportsmen.

The authors' proposed method for diagnosing inguinal canal disruption does actually produce quite unpleasant pain in even the most stoical patient, but perhaps that is the intention.

Finally, should we now be referring to 'sportsperson's groin'?

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Author's reply

Sir

I am grateful for the opportunity to reply to Mr Benson's supportive letter referring to the difficulties and diagnosis of the sportsman's groin. We agree that an accurate diagnosis with particular reference to prehernia complex or 'footballer's hernia' does give an opportunity for a successful outcome following surgical repair.

The technique described for local examination of the groin, with particular reference to the inguinal canal, produces the most consistent clinical findings with the minimum discomfort. Stoicism is not a common attribute demonstrated by even the most hardened professional sportsman during examination of the inguinal canal.

A recent audit of the attendances at the sports injury clinic at this hospital confirmed that 97·5 per cent of patients presenting with groin pain were male and it is therefore truly a problem that relates to sportsmen rather than sportspersons.

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Randomized trial to study the effect of fundic mobilization on long-term results of Nissen fundoplication

Sir

Along with Luostarinen and Isolauri (*Br J Surg* 1999; **86**: 614–18), we await convincing prospective data regarding the optimal degree of fundal mobilization in total fundoplication for gastro-oesophageal reflux disease.

Interpretation of their study comparing total fundoplication with and without fundal mobilization is confounded by a number of problems. (1) As discussed in the paper the sample size is small (24 and 26 patients in each arm). (2) Follow-up time is variable (6–53 months). (3) An independent observer was not used to obtain postoperative symptom scores. (4) The degree of fundal mobilization performed is not fully outlined. Were posterior gastric vessels and adhesions divided during fundal mobilization? (5) The oesophageal hiatus was not routinely repaired. There is considerable evidence that hiatal repair should be performed routinely in laparoscopic antireflux surgery[1,2]. Indeed the benefits of hiatal repair to prevent wrap migration were identified before the laparoscopic era[3].

The question of optimal fundal mobilization and its relationship to reflux control and postoperative dysphagia requires an answer. We would encourage the authors to repeat this study with full fundal mobilization and routine hiatal closure.

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Authors' reply

Sir

We thank Dr Smith and colleagues for their interest in our article and agree that the question regarding the need for fundic mobilization during Nissen fundoplication is not yet fully settled. Nevertheless, all the existing data from randomized studies[1–4] have failed to show any benefit. Regarding their comments about possible problems in our study:

(1) There were only a few instances of missing long-term data: 82 per cent of the patients were followed for more than 24 months and 50 per cent for at least 36 months. Despite the fact that one of the operating surgeons obtained this data, there was an emphasis on objectivity. All patients were encouraged to report all possible symptoms and these were scored before knowledge of endoscopic observations.
(2) Mobilization of the fundus was full with ligation of all fundic vessels including short gastric vessels at the greater

curvature and any posterior vessels with posterior adhesions.
(3) The wraps were constructed according to the Rossetti modification using only the anterior fundic wall and this was probably the case with the Australian study[4].
(4) The traditional Rossetti-type operation did not routinely include hiatal repair but from personal observation and evidence from the literature we now routinely perform haitusplasty in open and laparoscopic antireflux surgery. The occurrence of intrathoracic wraps in the present study may have had an effect on the rate of wrap disruption and recurrence of reflux. It did not affect the postoperative symptoms of dysphagia, flatus or bloating. The results regarding these adverse effects remained the same whether these patients were omitted from the analysis or not.

To obtain definitive answers regarding the necessity of fundic mobilization requires sufficient numbers of patients, long follow-up, examinations made by independent observers and the use of objective measurements including endoscopy, pH recording, manometry and radionuclide transit study. The comparison should be between Rossetti-type anterior wall wrap without any mobilization and a fully mobilized fundic wrap constructed between posterior and anterior fundic walls.

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Thyroid surgery and the recurrent laryngeal nerve

Letter 1

Sir

Professor Wheeler has written an excellent clinical dilemma (*Br J Surg* 1999; **86**: 291–2) on how to find the recurrent laryngeal nerve, but not what to do if the nerve cannot be identified. I must admit to having difficulty in identifying the inferior cornu of the larynx and hopefully the nerve will have been identified before that entrance point. From a practical point of view, if the nerve is not seen lying superficial to the inferior thyroid artery, then presumably it must be lying deep to it, which is the more common situation. If the nerve is not apparent, painstaking dissection among the branches of the inferior thyroid artery is liable to cause bleeding with obscuration of the field and unnecessary use of diathermy, which in itself could damage the nerve. Knowing where it should be, is it not more practical simply to leave a thin sliver of thyroid gland at that site even where a total thyroidectomy is indicated? Not only will this protect the nerve, but probably a parathyroid gland which is commonly found at that site.

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Letter 2

Sir

We read with interest this clinical dilemma and would like to add another method of resolving such a dilemma. In conditions where it is impossible to identify the recurrent laryngeal nerve lateral to the thyroid lobe, such as in a scarred neck during reoperative surgery or where there is an adherent lateral lymph node mass obscuring the space lateral to the lobe, we have found the technique of 'medial to lateral' dissection very useful. A plane is created between the true capsule (the thyroid capsule) and the false capsule (pretracheal fascia) by dividing the isthmus in the midline. The thyroid lobe is then dissected off the trachea thereby leaving the recurrent laryngeal nerve safe deep to the pretracheal fascia. Once the thyroid lobe is completely dissected it is possible to visualize the nerve inferiorly and dissect it off the thyroid, tracing it to the point of its entry in the larynx.

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Author's reply

Sir

The letters from Dr Wise and Dr Agarwal and colleagues raise some interesting points. It is correctly stated by the first correspondent that the main thrust of the article was to describe how to find the recurrent laryngeal nerve and indeed it was hoped that the techniques described would enable the surgeon to locate the recurrent laryngeal nerve even in circumstances where this may be difficult or appear impossible. Attention to these steps and meticulous haemostasis and dissection in a bloodless field should make the unidentifiable recurrent laryngeal nerve an extremely rare entity.

I am surprised that there could be difficulty identifying the inferior cornu of the larynx as this is very easily palpable in almost all patients. This is a most important landmark and the site where most recurrent laryngeal nerve injuries occur. I disagree with the suggestion that if the nerve is not seen lying superficial to the inferior thyroid artery then it must inevitably be lying at a deeper level. Furthermore, leaving a remnant of thyroid tissue when a total thyroidectomy is indicated may in some circumstances compromise the treatment of a thyroid malignancy.

The technique described by Dr Agarwal and colleagues, to dissect the thyroid lobe from medial to lateral creating a plane between the thyroid capsule and the pretracheal fascia, is a method of which I have no personal experience and may be of value.

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Epidemiology of Warthin's tumour of the parotid gland in an Asian population

Sir

The study by Dr Chung and colleagues (*Br J Surg* 1999; **86**: 661–4) adds further evidence of an association between smoking and Warthin's tumour of the parotid gland. They used the opportunity of a national smoking control programme to test the hypothesis that the relationship may be reversed following a decline in smoking consumption. The study failed to demonstrate a decline in incidence which probably reflects the short study period (10 years). The long-term observation of the incidence of Warthin's tumour in this well defined Singaporean population warrants our future attention.

What is intriguing is the finding of an apparent increased incidence of Warthin's tumour in the Chinese population (26 per cent of all parotid tumours compared with 17 per cent in Western populations[1]), especially in the light of recent evidence linking Epstein–Barr virus (EBV) and Warthin's tumour, recognizing that EBV infection is endemic in South-East Asia. The evidence linking EBV and Warthin's tumour comes from two principle observations: the detection of EBV DNA in tumour cells using *in situ* hybridization[2] and polymerase chain reaction technology[3] and the reporting of higher levels of EBV viral capsid antigen (VCA) immunoglobulin (Ig) G and EBV early antigen IgG in patients with Warthin's tumour compared with healthy subjects[4].

EBV and smoking may act together and be central to the pathogenesis of Warthin's tumour. Interestingly, malignant transformation of this salivary tumour is exceedingly rare, in contrast to pleomorphic adenoma where there is a recognized (albeit small) risk[5]. If the role of EBV is confirmed and the causative association with smoking substantiated, one future question is why these agents result in the development of a benign parotid tumour, yet induce malignancy in so many other neoplastic processes.

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Author's reply

Sir

Mr Renehan and colleagues offer the hypothesis that EBV may be an aetiological agent in the development of Warthin's tumour. As a matter of fact, we are examining this possibility and will be publishing our data in due course.

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Adrenal-sparing surgery for phaeochromocytoma

Sir

We read with some concern the article by Neumann and colleagues (*Br J Surg* 1999; **86**: 94–7) describing an experience with 'adrenal-sparing' surgery for phaeochromocytoma and consider this therapeutic approach to be less than prudent. Over the past 10 years we have operated on 75 patients for either sporadic or hereditary phaeochromocytoma and believe that the risk of recurrence or the chance of leaving a nest of tumour cells outweighs the dubious benefit of leaving cortical tissue in place.

Most often a complete unilateral resection is all that is required and the contralateral gland remains intact. Bilateral adrenalectomy may be necessary in some patients but this is preferable to recurrence. Adrenal insufficiency is a treatable entity.

Early in our experience, we attempted to 'preserve' cortical tissue in a woman with multiple endocrine neoplasia type 2a. Some years later, she developed tumour recurrence in the hepatorenal pouch with infiltration in the liver, diaphragm and vena cava. The attempt to conserve tissue might have been the cause of the patient's later inoperable state.

We believe that there is no fixed boundary between the cortex and the medulla[1] and the surgeon cannot demarcate one from the other. The pathologist often finds nests of medullary tissue in the cortex. Given this experience and the current knowledge of the gland's histology, we are uneasy about the approach of Neumann and colleagues and feel that total resection of the ipsilateral gland remains the most prudent course.

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Author's reply

Sir

We thank Dr Iacconi and colleagues for their interest in our paper and for describing their results. However, they do not provide exact data on how many patients had adrenal-sparing surgery, or how many had multiple endocrine neoplasia (MEN) type 2, Von Hippel–Lindau disease (VHL) or sporadic tumours. Their criticism is based on a single patient with MEN 2a and an inoperable phaeochromocytoma with infiltration of surrounding tissues. Malignant phaeochromocytoma is an extremely rare condition in MEN 2.

The high risk of bilateral adrenal tumours in MEN 2 and VHL disease leading to total resection of affected adrenals as suggested means loss of adrenocortical function at a young age. The statement that 'adrenal insufficiency is a treatable entity' is not trivial. In addition to steroid dependency there are the risks of undersupplementation and oversupplementation.

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Laparoscopic management of complicated gallstone disease

Sir

I read with interest the leading article by Geoghegan and Keane (*Br J Surg* 1999; **86**: 145–6) in which they propose three strategies for the management of choledocholithiasis: (1) for low-risk patients no preoperative or intraoperative cholangiography; (2) for medium-risk patients intraoperative cholangiography followed by laparoscopic exploration of the bile duct; and (3) for high-risk patients needing preoperative endoscopic retrograde cholangiopancreatography (ERCP).

I have reservations regarding their conclusions for groups 1 and 2. Intraoperative cholangiography followed by laparoscopic exploration of the bile duct for the medium-risk patient could not be accomplished by many surgeons. The skills required for exploring a 5–10-mm duct are not within the capabilities of most surgeons involved with laparoscopic surgery and will continue to be practised only in specialist centres.

One of the main reasons for suggesting this approach is the reduced postoperative stay and cost as compared with laparoscopic cholecystectomy plus postoperative ERCP. Peroperative ERCP can be used for patients in the low to medium groups[1] and high-risk group[2] as this shares, with laparoscopic common bile duct (CBD) exploration, the benefits of reduced hospital stay, cost and patient discomfort at having to undergo a second procedure in the immediate postoperative period.

I feel that patients strongly suspected to have CBD stones should have preoperative ERCP and all others should undergo preoperative or peroperative cholangiography. If stones are found an attempt should be made to extract them transcystically. If this fails, peroperative ERCP should be attempted and can be combined with the transcystic approach. If this is unsuccessful open exploration is advised.

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2 Cox MN, Wilson TG, Toouli J. Peroperative ERCP during laparoscopic cholecystectomy for choledocholithiasis. *Br J Surg* 1995, **82**: 257–9.

Peripheral thrombolysis for acute-onset claudication

Sir

Braithwaite and colleagues reviewed their experience of thrombolysis for acute-onset claudication (*Br J Surg* 1999; **86**: 800–4). Two of the reported deaths were due to renal failure and we suspect these patients died from ischaemia-reperfusion syndrome, a complication that we have also encountered following thrombolysis. We need to be vigilant about the development of the reperfusion syndrome following thrombolysis and embolectomy and need to remember that prompt amputation of the reperfused limb may be life saving.

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Chronic groin sepsis following tension-free inguinal hernioplasty

Sir

Messrs Taylor and O'Dwyer (*Br J Surg* 1999; **86**: 562–5) fall short of concluding that a multifilament mesh may not be used for inguinal hernioplasty for the reasons outlined in their discussion. We have performed over 400 inguinal hernia repairs with such a mesh in the past 5 years without any complication of mesh infection. A monofilament prosthetic mesh should be the material of first choice for inguinal hernioplasty[1].

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During liver regeneration following right portal vein embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma

Sir

We read with interest the paper by Elias and colleagues (*Br J Surg* 1999; **86**: 784–8) and wish to make the following comments. Malignancy in general can be characterized by unbalanced growth and apoptosis. As the study examined the tumours at only two time points it is not possible to say that the lesions were not continuing along a previously biologically determined growth-line. This would also account for the idiosyncratic responses observed both between and within individuals as the authors discuss. Without having knowledge of the growth rates for an individual tumour it would be premature to conclude that portal vein embolization *per se* had any direct effect on individual tumour growth.

In their discussion the authors cite two papers[1,2] implicating transforming growth factor α as a potential mediator. Both papers, however, were concerned with the growth responses of tumours derived from the liver rather than from elsewhere. Primary tumours derived from liver are likely to have similar endocrine responses to normal liver, whereas metastatic lesions are likely to differ (indeed one patient's tumour was reduced in volume). There were 48 patients who underwent right portal vein embolization (RPVE), only five of whom had metastatic disease and these tumours showed varied growth rates. It may have been more appropriate to determine the responses in the 43 patients who had primary liver tumours rather that the smaller subset with metastases.

We are also concerned that the method chosen for volume estimation may not be altogether reliable. The authors have not stated that the computed tomography (CT) images were obtained in a single breath-hold as this is required for accurate volume measurements. The use of CT contrast was inconsistent. Contrast enhancement in scans after RPVE could have led to the enhancement of tumour not distinguishable in the preliminary scans without contrast but nevertheless present.

We share the same oncological concerns regarding use of portal vein embolization to extend the indications for surgery. At present, the evidence for adverse effects is insufficient to withhold its use when faced with otherwise rapidly fatal disease with no good alternatives for palliation.

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1 Seki S, Kawakita N, Yanai A, Sakaguchi H, Kitada T, Nakatani K *et al.* Transforming growth factor-alpha causes proliferation of human hepatocellular carcinoma. *Gastroenterology* 1994; **106**(Suppl)· 980 (Abstract).
2 Lee GE, Merlino G, Fausto N. Development of liver tumours in transforming growth factor alpha transgenic mice *Cancer Res* 1992; **52**: 5162–70.

Author's reply

Sir

We thank Messrs Seymour, Manas and Charnley for their interest in our article. The objective of our work was to examine the differential growth patterns of metastases and surrounding normal parenchyma following right portal vein embolization. We propose possible explanations and accept the comments of Seymour *et al.* It is incorrect, however, to state that only five of 48 patients undergoing embolization had metastatic disease. All had extensive right hepatic metastases and only five had metastatic disease in the remaining left liver. Preoperative hypertrophy may have been on-going. Right portal vein embolization induced a relative atrophy of the embolized liver and it was illogical to determine growth rates in this part of the liver.

In our judgement the adverse effects are not sufficient to suggest withholding this treatment. We believe it may have contributed to the 5-year survival rate of 28 per cent after hepatectomy.

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Physiological comparison of open and endovascular aneurysm repair

Sir

We read the article by Treharne and colleagues (*Br J Surg* 1999; **86**: 760–4) with great interest but are puzzled at the operative severity scores quoted in the conventional group. Using the operative severity scoring table (*Table 1*) provided in the article we could not see how a mean score of 26·3 could be reached when all of the patients were elective and only eight required further procedures.

Looking at *Table 2* all patients would have scored 8 in line 1. In lines 4, 5 and 6 all patients would have scored 1 point each, assuming none of the patients had concurrent malignant disease. Eighty-one of the 104 patients in the conventional group had blood loss greater than 1000 ml, scoring 8 each, and we would assume that the remaining 23 scored 4 points each for blood loss. Using these figures and allowing 8 points each for the eight patients who underwent further procedures, we found the average score to be 19·7. This is the same as the mean severity score quoted for the endovascular procedures.

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Authors' reply

Sir

The operative severity scores were significantly higher in the conventional group because all patients had peroperative blood contamination of the peritoneal cavity and therefore scored 8. The conventional group also had higher levels of peroperative blood loss than the endovascular group and a greater number of additional surgical procedures performed. Mr Mahon and colleagues are correct in calculating that this alone would not be sufficient to raise the operative severity score significantly. The original paper on the subject by Copeland *et al.*[1] is unclear on whether blood contamination should be recorded at the start of the operation or at the end, as this clearly has a significant effect on the operative severity score and therefore the expected mortality.

We feel that this point should not detract from the central message of the paper that in physiologically matched patients, endovascular abdominal aortic aneurysm (AAA) repair was found to be associated with lower morbidity and mortality rates than conventional AAA repair. Indeed, since publication of this paper, we have found that mortality for conventional AAA repair (in patients originally referred for possible endovascular repair) was almost directly proportional to the Portsmouth Physiological and Operative Severity Score for enUmeration of Morbidity and mortality (P-POSSUM) score when this was stratified (*Table 1*) and we now calculate P-POSSUM scores on all patients who are being considered for AAA repair in an attempt to predict the risk of death. We feel that this may be a useful adjunct to clinical assessment, particularly as it can be used to quantify risk.

Table 1 Mortality rates for conventional AAA repair according to P-POSSUM score (overall mortality 16·3 per cent)

Physiological score	No. of patients	Mortality rate (%)
0–15	0 of 18	0
16–20	4 of 35	11
21–25	7 of 16	44
>25	6 of 8	75

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1 Copeland GP, Jones D, Walters M. POSSUM: a scoring system for surgical audit. *Br J Surg* 1991; **78**. 356–60.

Identification of patients likely to benefit from biofeedback for outlet obstruction constipation

Sir

When biofeedback was first described as a treatment for constipation, the success rates ranged from 87 per cent[1] to 100 per cent[2–4]. In most of the earlier series patients were chosen in whom the only diagnosis was paradoxical puborectalis contraction (PPC, anismus). As more experience has been gained the indications have broadened and it is not uncommon for patients to be referred when no other treatment is suitable[5]. It is, therefore, not surprising that more recent success rates have ranged from 29 to 63 per cent[6–10]. In our recent study[7] of 194 patients (median age 71 years), 63 per cent who completed the treatment protocol experienced complete success while this occurred in only 25 per cent of those who self-discharged from therapy ($P < 0{\cdot}0001$). The success rate for biofeedback for patients with constipation was less than previously reported, but did improve if patients were willing to complete treatment. McKee *et al.* (*Br J Surg* 1999; **86**: 355–9) find that biofeedback for outlet obstruction is more likely to be successful in patients without evidence of severe pelvic floor damage.

Biofeedback will undoubtedly continue to serve an important role in the treatment of patients with PPC, especially if selected through a variety of careful physiological and psychological tests. These individuals appear to be well motivated and without pelvic floor damage. Individuals with more severe degrees of PPC may be better treated by botulinum toxin[11,12]. Patients with severe psychological disturbances may derive benefit from psychological counselling[13]. The large group in whom increased perineal descent, rectocele, rectoanal intussusception and sensory abnormalities are also present may not derive any benefit[14]. Biofeedback remains morbidity-free and outpatient-based and allows the patient access to therapists who can devote time and energy to provide psychological guidance, counselling and muscular training.

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1 Kawimbe BM, Papachryotomou M, Binnie NR, Clare N, Smith AN. Outlet obstruction (anismus) managed by biofeedback. *Gut* 1991; **32**: 1175–9.
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Erratum

P. P. Tekkis, A. J. E. Bentley, H. M. Kocher, L. M. South, G. A. Trotter. Risk scoring in surgical patients. *Br J Surg* 1999; **86**: 1225 (Letter). Please note H. M. Kocher's correct initials.

Book review

Surgery at a Glance

P. A. Grace and N. R. Borley

275 × 219 mm. Pp. 163 Illustrated. 1999. Oxford: Blackwell Science. Price not supplied.

This delightful book is the latest in the *At a Glance* series and only the second on a purely clinical subject. It follows the established pattern of the series with each topic covered by two pages, a conceptual diagram on the left-hand page and text on the right. The quality of the diagrams is such that for the majority of the topics the text is almost superfluous. General surgery and urology are covered in comprehensive fashion. There are sections on fractures and arthritis outlining basic principles, but orthopaedic knowledge would need supplementing from elsewhere. Curiously, there is a section on the acute red eye and it is difficult to understand why this has been included. It is aimed primarily at medical students, but any trainee who could reiterate its contents should have little difficulty with the clinical aspects of the Royal College of Surgeons of England membership examination. If you learn easily from diagrams this is the book for you. For senior staff involved with teaching much could be gained from reading this volume and then adopting a similar approach in sessions with the students.

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Scientific Surgery

Cohn SM, Moller BA, Feinstein AJ, Burns GA, Ginzburg E, Hammers LW. Prospective trial of low molecular weight heparin *versus* unfractionated heparin in moderately injured patients. *Vasc Surg* 1999; **33**: 219–23.

Some 104 patients with moderate injuries were randomized. Only two patients developed a deep vein thrombosis on ultrasonography, both after unfractionated heparin. There were five major bleeding complications in each group

Fossati R, Confalonieri C, Torri V *et al.* Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *J Clin Oncol* 1998: **16**: 3439–60.

This summary of 12 treatment comparisons reveals scant evidence of effectiveness with only modest survival benefits. Quality of life data were sparse.

Lobo DN, Riddick ACP, Iftikhar SY, Gudgeon AM. Home rectal evacuation prior to a colorectal clinic appointment: a prospective, randomized controlled, single-blind trial. *Colorectal Dis* 1999; **1**: 158–61.

Three groups of 50 patients were randomized to self-administered home microenema, glycerine suppositories or control groups. Views with a rigid sigmoidoscope were best after the suppositories

Taylor DW, Barnett HJM, Haynes BR, Ferguson GG, Sackett DL, Thorpe KE *et al.* Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999; **353**: 2179–84.

Some 2849 patients having carotid surgery were assigned one of four different aspirin doses Combined rate of stroke, myocardial infarction or death was less after lower dose aspirin (81 or 325 mg (5·4 per cent)) than higher dose aspirin (650 or 1300 mg aspirin daily (7 per cent, $P = 0·07$))

Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E *et al.* Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999; **353**: 1993–2000.

A total of 1804 women who had lumpectomy and radiotherapy for ductal carcinoma *in situ* were randomly assigned additional tamoxifen The incidence of 'breast cancer events' after 5 years was lower in the tamoxifen group (8·2 *versus* 13·4 per cent, $P = 0·001$).

Peterson S, Hellmich G, Baumann M, Herrmann T, Henke G, Ludwig K. Preoperative radiotherapy in the treatment of rectal cancer: long term results of a prospective randomized trial. *Chirurg* 1998; **69**: 759–65.

Ninety-three patients were randomized. Preoperative radiotherapy improved 5-year survival ($P = 0·027$) and the local recurrence rate ($P = 0·08$)

Izbicki JR, Gawad KA, Quirrenbach S, Hosch SB, Breid V, Knoefel WT *et al.* Can stapled anastomosis in visceral surgery still be justified? A prospective controlled randomized study of the cost-effectiveness of hand-sewn and stapled anastomoses. *Chirurg* 1998; **69**: 725–34.

This study included 324 anastomoses in 200 patients having a variety of different bowel resections. Stapled anastomoses were quicker but more expensive. Stapling did not reduce complication rates (anastomosis leak rate 2·1 per cent) or hospital stay.

Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH, Welvaart K, Songun I *et al.* Extended lymph node dissection for gastric cancer. *N Engl J Med* 1999; **340**: 908–14.

Some 711 patients having curative resection were randomly assigned to extended or routine lymph node dissection. Extended dissection increased perioperative mortality (10 *versus* 4 per cent, $P = 0·004$) and complications (43 *versus* 25 per cent, $P < 0·001$) but the 5-year survival rate was similar (47 *versus* 45 per cent respectively)

Ballotta E, Da Giau G, Saladini M, Abbruzzese E, Renon L, Toniato A. Carotid endarterectomy with patch closure *versus* carotid eversion endarterectomy and reimplantation. A prospective randomized study. *Surgery* 1999; **125**: 271–9.

The study included 336 operations Eversion endarterectomy resulted in fewer perioperative deaths (3 *versus* 0, P not significant), fewer perioperative strokes (5 *versus* 0, $P = 0·03$) and fewer late recurrent stenoses/occlusions (5 per cent *versus* none, $P = 0·003$)

Ingle JN, Suman V, Kardinal CG, Krook JE, Mailliard JA, Veeder MH *et al* A randomized trial of tamoxifen alone or combined with octreotide in the treatment of women with metastatic breast cancer. *Cancer* 1999; **85**: 1284–92.

In this study of 135 women, the addition of octreotide did not improve the response rate (43 *versus* 49 per cent with tamoxifen alone) or survival (death hazard ratio 0·98, 95 per cent confidence interval 0·62–1·55)

Durkin MT, Turton EPL, Scott DJA, Berridge DC. A prospective randomised trial of PIN *versus* conventional stripping in varicose vein surgery. *Ann R Coll Surg Engl* 1999; **81**: 171–4.

There was no significant advantage to using the Perforate Invagination stripping method apart from a smaller exit wound at the knee in this study of 80 patients.

Sutton CD, White SA, Edwards R, Lewis MH. A prospective controlled trial of the efficacy of isopropyl alcohol wipes before venesection in surgical patients. *Ann R Coll Surg Engl* 1999; **81**: 183–6.

The use of the alcohol swab had no effect on wound complications in 194 procedures two patients developed an abscess, both after skin swab preparation.

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The *British Journal of Surgery* ISSN 0007-1323

Published on behalf of the British Journal of Surgery Society. All queries regarding submitted papers not yet accepted for publication should be addressed to:
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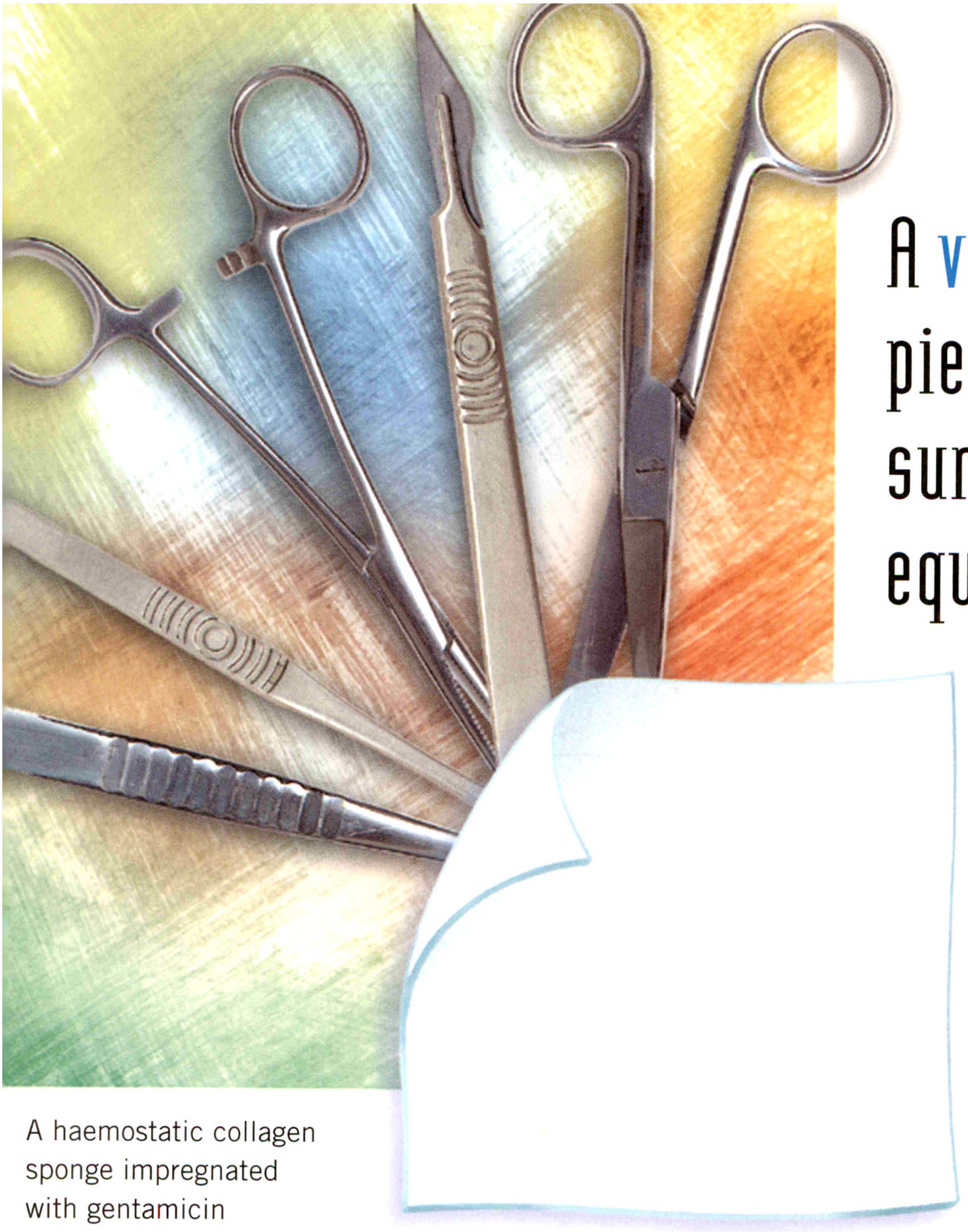

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Leading article

Flat adenomas

A. Cairns and P. Quirke

University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds LS1 3EX, UK

Flat adenomas were first described in 1985 when Muto *et al.*[1] reported a series of 33 cases. They are easily missed at endoscopy, presenting as small reddish spots with or without a central depression. On microscopic examination they are usually seen to be tubular adenomas, with the adenomatous component being no more than twice the height of the adjacent normal mucosa[1,2]. The underlying muscularis mucosae has been described as thin and loose, supposedly providing little barrier to invasion by adenocarcinoma[1].

Despite reports emerging from Japan, Western endoscopists and pathologists at first remained sceptical about the occurrence of flat adenomas in Western populations. The first reports of flat adenomas in the West did not appear until Lynch *et al.*[3] described such lesions in a family under investigation for hereditary non-polyposis colorectal cancer. Reports from countries including Canada[2], Sweden[4] and, more recently, the UK[5,6] followed, confirming that flat adenomas do indeed exist in Western populations and are not solely an Eastern phenomenon.

The prevalence of these lesions is unknown. Reports are difficult to compare because there are differences in terminology between the West and the East, and differences in sample populations. In the experience of Muto and colleagues[1], up to 10 per cent of all adenomas are flat, while in the study by Kubota *et al.*[7] non-polypoid adenomas accounted for almost 20 per cent of adenomas found in 300 surgical resection specimens. In the West, flat adenomas accounted for 8·5 per cent of adenomas in 8·6 per cent of the patients studied by Wolber and Owen[2]. Jaramillo *et al.*[4] found 109 flat neoplastic lesions in 24 per cent of 232 patients. Fujii *et al.*[5] reported 28 non-polypoid adenomas in 208 consecutive colonoscopies, accounting for 41 per cent of adenomas. Hart *et al.*[6] found only four flat adenomas (one of which contained a focus of adenocarcinoma) in 3000 UK patients, although as this was a flexible sigmoidoscopy study the patients were all asymptomatic and the entire colon was not examined. The location of flat adenomas within the colon is also not well documented, but the transverse, descending and sigmoid colon seem to be preferred sites[7,8].

Why have reports of flat adenomas been slow to emerge in the West? One possibility is a problem of terminology, with Western endoscopists and pathologists removing and reporting these lesions but not categorizing them separately as flat adenomas. Another possibility is that Western endoscopists, traditionally trained to observe polypoid adenomas, are simply overlooking the flat lesions. Flat adenomas are notoriously difficult to identify, but visualization can be improved by ensuring good bowel preparation, and using techniques such as dye spraying and magnifying colonoscopy (with an experienced endoscopist, preferably one trained in Japan). Dye spraying and magnifying colonoscopy are not routinely used in the West and, indeed, many Japanese workers would cite this as the principal reason why flat adenomas have not been reported as frequently. Series that make use of Japanese techniques in Western populations report a higher incidence of flat adenomas than series that do not[4,5].

The advent of the flat adenoma has forced a review of current knowledge concerning the development of colorectal cancer. The concept that the majority of colorectal cancers arise from polypoid adenomas, known as the adenoma–carcinoma sequence, is well documented and widely accepted. Yet discrepancies in this model have been recognized for some time, notably the lack of an adenomatous component adjacent to some tumours, differing distribution of adenomas and carcinomas, and carcinomas developing where no precursor lesions had been identified. It has been suggested that some of these cancers may arise *de novo*, that is from normal colonic mucosa, without the intervening phase of a polypoid adenoma. The flat adenoma is a prime candidate for a precursor of such carcinomas and, indeed, there are reports of flat adenomas adjacent to flat cancers. Wada *et al.*[9] identified flat adenomatous tissue in association with 21–32 per cent of flat cancers.

There is some evidence to suggest that flat adenomas are more aggressive than polyps. In contrast to polypoid adenomas, small flat adenomas show a high proportion of severe dysplasia, up to 42 per cent[1] in some series. Wolber and Owen[2] noted that flat adenomas were ten times more likely to contain high-grade dysplasia than polypoid adenomas. p53 overexpression has also been reported by some authors[9,10].

In summary, despite early scepticism, flat adenomas do exist in Western populations and undoubtedly play an important role in the development of some colorectal cancers. The prevalence and natural history of these lesions have not yet been fully elucidated and further research is required. The discovery of flat adenomas and flat carcinomas is disconcerting for those involved in colorectal cancer surveillance and has important implications for colorectal cancer screening programmes.

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A patient declines mastectomy

A 40-year-old woman with a small breast cancer and extensive ductal carcinoma in situ *(DCIS) on mammography refuses mastectomy. What considerations apply to the best management of such a situation? Mr Dick Rainsbury of the Royal Hampshire County Hospital, Winchester, UK, replies.*

Surprisingly few patients question conventional medical advice or refuse treatment in today's climate of evidence-based patient choice. Still, a mastectomy may occasionally be refused and for very different reasons, but lack of understanding, inadequate information, poor communication and fear of mutilation are common factors. The problem may be compounded by inappropriate advice about surgical options. Faced with this dilemma, the surgeon has a dual responsibility to respect the patient's viewpoint and to review three key aspects of investigation and management with her: treatment options and risks, avoiding local recurrence, and limiting cosmetic deformity.

Treatment options and risks

Informed advice about treatment requires complete histopathological data and multidisciplinary review in order to establish the extent of disease, treatment options and prognosis. This cannot be based on tumour size and radiological appearance alone. Consider two premenopausal women with identical mammograms showing segmental microcalcification around a small carcinoma which has been confirmed by triple assessment. The first patient has a 1-cm, grade 3, node-positive, oestrogen receptor (ER)-negative ductal carcinoma surrounded by intermediate-grade, non-comedo DCIS and benign segmental microcalcification. The DCIS has been excised with 10-mm margins and the invasive tumour scores 6·2 using the Nottingham Prognostic Index (NPI)[1], predicting a 15-year survival rate of less than 15 per cent. The second patient has a 1-cm, grade 1, node-negative, ER-positive ductal carcinoma, associated with extensive intraductal carcinoma (EIC) and malignant microcalcifications which abut the resection margin in several places. The NPI is 2·2, predicting a 15-year survival rate of over 90 per cent.

Treatment of the first patient must focus on reducing the considerable risk of metastasis and death. The life-time risk of local recurrence is very small and marked deformity resulting from extensive local excision can be avoided. It is the second patient who presents the real dilemma. She carries a considerable life-time risk of local recurrence because of her near-normal life expectancy and major risk factors for such recurrence (EIC, positive margins[2]). Treatment must be focused on reducing local recurrence by mastectomy or extensive re-excision, but both lead to marked deformity.

Effective communication of the type of risk in each case may be hampered by the disproportionate emotional sensitivity experienced by many patients who equate the need for mastectomy with a dire prognosis. Confusing concepts, such as the favourable prognosis of 'extensive' DCIS and the paradoxical need for radical treatment in spite of early disease, demand careful and repeated explanation. Too much information can lead to confusion about essential details such as invasion, local recurrence and metastasis, and the specialist nurse plays a pivotal role as patient advocate and confidante. By identifying areas of doubt, uncertainty and misunderstanding, concerns about treatment can be addressed and resolved at an early stage.

Avoiding local recurrence

Selecting an approach which limits local recurrence while avoiding severe deformity is the key to resolving this clinical dilemma. Minimizing risks of recurrence requires careful preoperative investigation, peroperative specimen orientation and radiology, and postoperative margin and cavity wall analysis, providing essential data to inform both surgeon and patient about treatment options. A stepwise approach will help the patient to understand the limitations of breast-conserving surgery and allow the surgeon to give advice based on hard data.

In a patient with a small 'minimally invasive' cancer (1–10 mm), decisions about the appropriateness of breast-conserving surgery will hinge on the adequacy of excision of the surrounding DCIS. Resection can be enhanced by high-quality mammography, ultrasonography and magnetic resonance imaging which help to exclude rare multicentric disease and to delineate non-calcifying DCIS. Using an index based on DCIS grade, size and margins (Van Nuys Prognostic Index[3]) will help to identify those patients who can safely avoid mastectomy or radiotherapy. Radiotherapy after limited excision of DCIS reduces local recurrence by 50 per cent[4] and tamoxifen adds further to this benefit[5], but similar rates can be achieved by wider excision alone[6], avoiding adjuvant treatment but risking volume loss and deformity. Patients should be informed of their personal risk of local recurrence, and that 50 per cent of such recurrence after breast-conserving surgery is invasive – a risk virtually eliminated by mastectomy.

Limiting cosmetic deformity

Breast deformity is a major issue for many patients and its probability is related to tumour position, specimen size and breast volume. Deformity during breast-conserving surgery can be avoided by using volume replacement with myocutaneous or myosubcutaneous flaps, or volume displacement with dermoglandular flaps to fill resection defects. Furthermore, a 'mirror-image' reduction of the contralateral breast can restore symmetry when treating upper outer quadrant tumours. Familiarity with these techniques facilitates wide margin-free resection of up to 50 per cent of the breast volume during conserving surgery without significant cosmetic penalty[7].

When mastectomy is unavoidable because of widespread, multicentric or subareolar disease, immediate and delayed reconstruction should be discussed. The patient outlined in this clinical dilemma would benefit from comprehensive information and advice, and an opportunity to meet others who have undergone reconstruction. Moreover, skin-conserving techniques combined with myocutaneous reconstruction can now achieve life-like glandular replacement within the native skin envelope, without increasing complications or local recurrence[8].

An approach which combines risk assessment with risk reduction and the avoidance of deformity by appropriate reconstruction will go some way towards resolving the dilemma. A second opinion should be sought if these steps fail to resolve any lingering doubts and uncertainties.

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Review

Combined inguinal and pelvic lymph node dissection for stage III melanoma

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Background: The incidence of melanoma is increasing in the UK and a significant number of patients are still presenting with primary lesions of poor prognosis. As a consequence there is likely to be an increasing number of patients with lymph node metastases for whom the appropriate extent of groin dissection remains controversial. This review summarizes the evidence to enable surgeons to make an informed decision about the management of patients with melanoma metastases to the groin lymph nodes.

Methods: A Medline search was performed to identify all English language articles about melanoma containing the words lymphadenectomy, lymph nodes, inguinal or lymphoedema. Eighty-seven relevant articles were selected from 3904 abstracts retrieved; 34 were related directly to the aim of this review.

Results: There are no randomized controlled trials comparing the outcome of combined inguinal and pelvic lymph node dissection (CLND) and superficial inguinal lymph node dissection (SLND). Excision of pelvic lymph node metastases is reported to yield a 5-year survival rate of 0–35 per cent. Recurrence within the pelvis occurs in 9–18 per cent of patients after SLND and in less than 5 per cent after CLND. Morbidity following either CLND or SLND is poorly reported. Major long-term lymphoedema limiting patient activity affects 6–20 per cent of patients after groin dissection. Cloquet's node was demonstrated in one study to be a useful predictor of pelvic lymph node involvement. Patients may be selected for pelvic node dissection on the basis of clinical findings, the results of pelvic computed tomography and the status of Cloquet's node.

Conclusion: The controversy surrounding the appropriate management of cytologically positive inguinal nodes in melanoma can be resolved only by a prospective randomized trial comparing CLND with SLND. Morbidity and local disease control must be measured as outcomes in addition to disease-free and overall survival.

Paper accepted 31 August 1999

British Journal of Surgery 1999, 86, 1493–1498

Introduction

Controversy and uncertainty remain about the appropriate management of patients with regional melanoma metastases to the groin. There is an extensive literature on elective lymph node dissection for stage I and II disease and, more recently, on the role of sentinel lymph node biopsy to detect occult lymph node metastases. However, the extent of surgery for patients with known inguinal melanoma metastases has drawn less attention.

There are sharply conflicting views on the role of pelvic lymph node dissection (PLND) as an extension of inguinal lymphadenectomy. Pelvic node clearance includes at a minimum dissection of the external iliac and obturator lymph node groups[1,2], and for that reason the terms 'iliac' and 'ilioinguinal dissection' are regarded as misleading. Some authors argue that PLND should not be performed as it carries an increased morbidity with no improvement in overall or symptom-free survival rates[3–7]. Others have found a therapeutic benefit with little difference in morbidity[8–10]. In the middle ground, studies have found a small group of patients who may have benefited from PLND[11–15]. This article reviews the published results on combined superficial inguinal and pelvic lymph node dissection (CLND) for stage III melanoma in the groin. As with any intervention in oncology, the outcome of the surgical management of groin lymph node metastases must be measured in terms of survival benefit, recurrence rate, symptom control and morbidity. This review also examines factors that may allow selection of patients for CLND.

Survival

The detractors of CLND recognize no survival benefit of the more extensive procedure over superficial inguinal lymph node dissection (SLND). Their impression is that pelvic nodal involvement indicates an advanced stage of disease in which systemic spread is inevitable; the advanced pelvic node component rarely becomes an issue of clinical relevance. The survival of patients with positive pelvic nodes following CLND is presented in *Table 1*. In 1989 Coit and Brennan[4] tabulated the survival of patients with positive pelvic nodes from the seven studies available at that time, including their own results. Thirteen (8 per cent) of 156 patients survived for more than 5 years. A significant proportion of patients in these studies was deemed to have had palliative rather than therapeutic resection, that is patients had stage IV disease at the time of operation.

Kissin *et al.*[13], in 1987, reported a 25 per cent 5-year survival rate for patients with one involved pelvic node, a rate that dropped to 14 per cent if two nodes were involved. Recently, Mann and Coit[6] presented new data from Memorial Sloan-Kettering Cancer Center on patients with involved pelvic nodes, showing a median survival of 19·5 months and a 5-year survival rate of 35 per cent. Karakousis and Driscoll[10] have updated the results from Roswell Park on a regular basis and have most recently described 48 patients with pelvic node metastases accrued over a period of 17 years. The overall 5-year survival rate was 34 per cent and the disease-free survival rate was 21 per cent. Survival was not related to the number of positive pelvic nodes. Strobbe *et al.*[15] recently presented a 25-year experience from Amsterdam. Over this period 71 patients were identified with positive pelvic nodes. The 5-year survival rate was 24 per cent and the 10-year rate 20 per cent. Unfortunately, the last three studies do not state the absolute number of 5-year survivors, but they do include relatively large numbers of patients with a long follow-up.

There has been no appropriately stratified randomized controlled trial to allow accurate assessment of the potential survival benefit of CLND over SLND. Mann and Coit[6] compared SLND and CLND in patients matched for prognostic factors and found no survival difference. However, patients undergoing CLND were selected on the basis of either clinical or radiological suspicion of pelvic nodal disease and so represented a poorer prognostic group.

Local symptomatic control

Proponents of CLND claim that the procedure offers better control of the disease in the nodal field. Their concern is that unresected involved pelvic lymph nodes will become symptomatic following therapeutic SLND. The potential extent of the problem may be estimated from available data. Approximately 25 per cent of patients having SLND for clinically and histologically positive groin nodes have unresected involved pelvic lymph nodes (*Table 2*). At least 50 per cent of these patients develop significant systemic disease and die within 18 months of groin dissection

Table 1 Survival of patients with melanoma metastases to pelvic lymph nodes

Reference	Year	Location	Study period	No. with positive pelvic nodes	Median survival (months)	No. surviving 5 years	Estimated 5-year survival (%)
Fortner *et al.*[11]	1964	MSKCC	1931–1956	46	NA	4	9
McCarthy *et al.*[3]	1974	Columbia University		4	NA	0	0
Das Gupta[16]	1977	Chicago	1968–1974	15		3*	20
Finck *et al.*[12]	1982	UCLA	1970–1980	24	20	4	17
Dasmahapatra and Karakousis[8]	1983	RPMI	1966–1977	10	NA	4	40
Karakousis and Driscoll[10]	1996	RPMI	1977–1993	48	NA	NA	34
Kissin *et al.*[13]	1987	RMH	1960–1983	1 node, 13	42	3	25
				2 nodes, 22	14	3	14
				> 2 nodes, 12	9	0	0
Jonk *et al.*[14]	1988	Netherlands	1961–1984	23	17	3‡	33
Coit and Brennan[4]	1989	MSKCC	1974–1984	19	12	1	6
Singletary *et al.*[5]	1992	MDACC	1948–1987	6	NA	0†	0†
Mann and Coit[6]	1999	MSKCC	1985–1994	22	19.5	NA	35
Strobbe *et al.*[15]	1999	Netherlands	1961–1995	71	NA	NA	24

*Eight patients in this group were not suitable for 5-year follow-up; †10-year survival figures; ‡six other patients were alive and metastasis-free at 6, 8, 19, 21, 24 and 28 months. MSKCC, Memorial Sloan-Kettering Cancer Center; UCLA, University of California at Los Angeles; RPMI, Roswell Park Memorial Institute; RMH, Royal Marsden Hospital; MDACC, M D Anderson Cancer Center; NA, not available

Table 2 Rate of pelvic lymph node involvement in patients with positive superficial nodes

		Positive at ELND		Positive at TLND		ELND + TLND		
Reference	Year	SLN	PLN	SLN	PLN	SLN	PLN	SLN negative, PLN positive
Fortner *et al.*[11]	1964					177	45 (25)	1
McCarthy *et al.*[3]	1974					9	2 (22)	2
Cohen *et al.*[7]	1975	5	0	18	3 (17)	23	3 (13)	
Das Gupta[16]	1977					33	8 (24)	7
Finck *et al.*[12]	1982	16	5 (31)	66	19 (29)	82	24 (29)*	
Dasmahapatra and Karakousis[8]	1983			22	10 (45)	22	10 (45)†	
Kissin *et al.*[13]	1987			131	45 (34)	131	45 (34)	2
Coit and Brennan[4]	1989	53	5 (9)	119	19 (16)	172	24 (14) ‡	1
Singletary *et al.*[5]	1992					131	6 (5)	0
Karakousis and Driscoll[9]	1994	40	8 (20)	80	34 (42)	120	42 (35)	
Mann and Coit[6]	1999			112	21 (19)	112	21 (19) §	1¶
Sterne *et al.*[17]	1995					25	13 (52)	
Total		114	18 (16)	548	151 (28)	1037	243 (23)	

Values in parentheses are percentages. *Patients were selected for pelvic lymph node dissection (PLND) on the basis of superficial lymph node (SLN) positivity. †Nine further patients had iliac lymph node biopsy; all were negative. Fifteen further patients had superficial lymph node dissection. The selection criteria were not stated. ‡Some 47 of 238 elective lymph node dissections (ELNDs) and 86 of 148 therapeutic lymph node dissections (TLNDs) included PLND. The rate of positive pelvic lymph nodes (PLNs) may be underestimated. §Of 113 TLNDs, 68 were superficial only; 22 of 45 therapeutic combined lymph node dissections were positive. ¶Three patients developed pelvic nodal recurrence after negative ELND

(*Table 1*). Therefore, it may be predicted that troublesome pelvic nodal involvement following therapeutic SLND would occur in no more than 12 per cent of patients at 18 months. Coit and Brennan[4] reported groin recurrence in 19 (9 per cent) of 203 patients who had positive dissections, with no difference between CLND ($n = 119$) and SLND ($n = 84$). Singletary *et al.*[5] evaluated 264 therapeutic groin dissections. Groin recurrence occurred after SLND in 31 (23 per cent) of 133 patients and after CLND in 12 (9 per cent) of 131 patients; only one patient developed symptomatic pelvic disease.

Mann and Coit[6] found among 113 patients undergoing therapeutic dissection that one (2 per cent) of 46 who had CLND and seven (9 per cent) of 77 who had SLND had recurrence first in the groin. The majority of these recurrences were successfully treated with further surgery. Calabro *et al.*[18] reviewed the pattern of relapse after 1001 positive lymph node dissections; 17 per cent of patients developed recurrence in the nodal field after groin dissection. Nodal recurrence was related to the number of positive nodes at the original dissection and the presence of extranodal spread. Harman *et al.*[19] described an 18 per cent pelvic node recurrence rate following 82 SLNDs and a 3 per cent recurrence rate following 98 CLNDs. Unfortunately, only the last of these studies have differentiated between wound and pelvic recurrence. The present authors conclude that there is some evidence to support CLND on the basis that it achieves significantly better local control of disease.

Morbidity

Inguinal lymph node dissection is associated with significant postoperative complications. There has been little progress in reducing the rate of wound infection or decreasing seroma formation. While adding PLND does not dramatically increase operating time in experienced hands[1,2], there is considerable concern that it increases both short- and long-term morbidity. As is the case with survival, these outcomes have not been assessed in a controlled trial. The reporting of complications and lymphoedema has tended to be subjective and variable between centres.

The risk of lymphoedema is one of the greatest concerns for patients who have been recommended an inguinal lymph node dissection; PLND is perceived to increase that risk greatly. Holmes *et al.*[20] evaluated 84 patients after groin dissection, selected for CLND on the basis of frozen section of suspicious superficial nodes. Lymphoedema was said to be present if the circumference of the operated leg exceeded that of the opposite by more than 2 cm. Twenty patients (24 per cent) had lymphoedema, which was present in the thigh alone in 11 cases. Eighteen patients reported some degree of limitation of activity but only three described serious alteration in their lifestyle. This study did not compare CLND with SLND. Urist *et al.*[21], using similar criteria, had similar findings; the problem relating to CLND could not be analysed as only two of 63 patients had CLND.

James[22] used volume displacement to assess lymphoedema after CLND; 80 per cent of patients had a difference of more than 100 ml in water displacement between legs, and in 30 per cent the difference was greater than 500 ml, with 25 per cent of all patients experiencing some limitation of activity. A further survey in which the assessment of lymphoedema was purely clinical recognized moderate to severe lymphoedema in 6·6 per cent of patients; CLND was the most significant risk factor but the actual number of patients was not provided in the report[22]. Interestingly, no increase in the rate of lymphoedema was observed in patients who had significant early postoperative morbidity. Baas *et al.*[23] reviewed 66 patients at a median of 4 years after CLND. Volume displacement was used to assess lymphoedema. Seven per cent of patients had more than a 20 per cent volume difference while 75 per cent had no significant difference between legs. Restriction of function was found in 9 per cent of the 66 patients.

Karakousis and Driscoll[9], who have one of the most extensive and well documented experiences with inguinal lymph node dissection for melanoma, have found no significant difference in wound complication or lymphoedema rates between CLND and SLND. Moderate to severe lymphoedema occurred in 12 per cent of their patients. These authors emphasize that, with appropriate advice and pre-emptive intervention, lymphoedema need not create a significant problem for the majority of patients. Patients should expect leg swelling in the first 6 months after operation and should wear a class II compression stocking which includes most of the thigh. It is apparent from the present review that there is little evidence to support the notion that CLND is associated with greater morbidity than SLND.

Predicting pelvic node positivity

The dilemma of whether to perform pelvic dissection or not for stage III melanoma affecting the groin is somewhat analogous to the dilemma that surrounds elective lymph node dissection for stage I and II melanoma. In clinical stage I and II melanoma the risk of occult nodal metastases is approximately 15–20 per cent and so only a relatively small proportion of patients could possibly benefit. Based on two prospective randomized trials of elective node dissection, the procedure has largely been abandoned[24,25]. The validity of these trials has reasonably been questioned because of lack of stratification for known prognostic factors[26]. Balch and co-workers[27] have demonstrated an advantage in some subgroups. Undoubtedly, the problem with elective node dissection has been that the subgroups of patients who might benefit have been difficult to define. The introduction of sentinel node biopsy may allow surgeons more easily to select patients with clinical stage I and II melanoma for lymph node dissection. The outcome of a randomized prospective multicentre trial is keenly awaited.

The surgeon dealing with stage III melanoma of the groin is confronted with a similar problem. Patients with histologically proven metastases to superficial inguinal lymph nodes have a 20–30 per cent chance of harbouring pelvic lymph node metastases (*Table 2*). It is this group of patients that would be most likely to obtain some benefit from PLND. Few studies have analysed the risk of pelvic node positivity when the superficial nodes are involved. Factors to consider include the clinical status of the groin, the number of positive superficial nodes involved, the status of lymph nodes in the femoral canal (Cloquet's nodes) and the results of preoperative computed tomography (CT) of the pelvis.

The clinical status of the groin before dissection is a crude measure of the extent of regional disease and as such is a useful indicator of pelvic node status. The introduction of sentinel node biopsy will probably raise the issue of appropriate management of a clinically negative and histologically positive groin. *Table 1* shows that few studies dealing with pelvic lymph node status have differentiated between clinical and subclinical superficial inguinal nodal involvement. In the available studies, pelvic nodes were positive in 18 (16 per cent) of 114 patients with histologically positive superficial inguinal lymph nodes following elective (prophylactic) CLND, and in 151 (28 per cent) of 548 patients with clinically involved inguinal nodes who had CLND. The difference in pelvic lymph node positivity between elective and therapeutic lymph node dissection is significant (χ^2 test, $P = 0{\cdot}03$). The usefulness of the clinical state of the groin as a selection factor has been questioned by Finck *et al.*[12], who found that three of four 5-year survivors following positive PLND had clinically negative groins. While the evidence available is inconclusive, clinically occult disease does not preclude a benefit from CLND. This has implications for the further surgical management of patients following a positive sentinel node biopsy. The rate of pelvic lymph node positivity following positive sentinel node biopsy is yet to be reported.

The relationship of the number of involved superficial inguinal nodes to the status of pelvic nodes may provide a more accurate tool for decision making. *Table 3* summarizes the available data. One positive superficial node carries a 15 per cent chance of lymph node involvement, two to three positive superficial nodes approximately a 25 per cent chance, and four or more positive nodes at least a 50 per cent

Table 3 Predicting pelvic node status by the number of involved superficial nodes

Reference	Year	No. of positive superficial nodes	No. of patients with positive pelvic nodes
Finck *et al.*[12]	1982	1	7 of 48
		2	4 of 16
		3	1 of 5
		4	5 of 10
		>4	7 of 15
Coit and Brennan[4]	1989	1–3	8 of 65
		≥4	11 of 25
Mann and Coit[6]	1999	1–3	8 of 25
		≥4	14 of 21
Sterne *et al.*[17]	1995	1	1 of 6
		2	2 of 8
		≥3	11 of 11

chance. It has been well documented that the number of involved inguinal lymph nodes is the most important prognostic factor in stage III disease; patients with four or more involved nodes have a 25 per cent 5-year survival rate compared with close to 50 per cent for those with three or less[13,28–31]. The poor outcome associated with CLND may be due to patient selection biased towards those with a greater number of involved superficial nodes and therefore an inherently poor outcome. It may well be that those with minimal inguinal disease are the group of patients who have the greatest chance of therapeutic benefit from CLND because of the lower risk of disseminated disease. Similarly, extranodal extension of the metastatic disease may encourage more heroic surgery. Unfortunately, this finding, irrespective of nodal number, decreases the 5-year survival rate to no more than 15 per cent[28].

Patients with an unknown primary have, with few exceptions, fared as well, if not better, than those with a known primary[14,28,29]. All three long-term survivors in the series presented by Jonk *et al.*[14] had unknown primaries. This phenomenon may recommend this unusual group of patients to an aggressive surgical approach.

The node of Cloquet is located in the femoral canal medial to the femoral vein. The histological status of the node may reflect the status of the pelvic lymph nodes and assist in selection of patients for PLND. Coit and Brennan[4] have evaluated the status of Cloquet's node as a marker of pelvic node disease; histological examination of Cloquet's node was negative for tumour in 60 cases and in 58 (97 per cent) of these cases there was no pelvic lymph node involvement. Of 24 patients with a positive Cloquet node, 19 (79 per cent) had positive pelvic nodes. Nevertheless, this impressive specificity of 92 per cent has not been reproduced in limited but more recent data[6] or in earlier work[32]. It seems appropriate for accurate assessment of Cloquet's nodes to be part of any ongoing evaluation of inguinal lymphadenectomy.

Many patients presenting for inguinal lymph node dissection will have been staged with abdominopelvic CT. The aims of CT are twofold. First, the detection of suspicious pelvic lymphadenopathy may effectively select patients for PLND with curative intent. Second, detection of sizeable pelvic metastases that are likely to become symptomatic would select patients for palliative PLND. Mann and Coit[6] selected patients for CLND on the basis of clinical or radiological suspicion of pelvic node disease; 21 of 45 therapeutic CLNDs yielded positive pelvic nodes. The present authors assume, given that all dissections were undertaken with curative intent, that the decision to perform CLND was based largely on CT findings. Seven of the 67 patients who had SLND relapsed in the pelvis.

Two recent studies have examined the role of CT in stage III melanoma[33,34]. It is apparent that the majority of patients with stage III melanoma at the respective institutions had CT. The true positive yields were small and were exceeded by the number of false positives. However, the question of pelvic scanning for the detection of pelvic lymphadenopathy was not addressed directly. Sterne *et al.*[17] evaluated CT in a sample of 16 patients having CLND. Three of eight positive scans were confirmed as true positives and seven of eight negatives as true negatives. Since scans of the pelvis are performed in most patients before lymphadenectomy and appear to be used to select patients for CLND, it is important that the sensitivity and specificity of this investigative technique are assessed in future studies.

Conclusion

CLND appears to carry a small but definite therapeutic benefit. The contention that increased morbidity results from CLND compared with SLND is not supported by evidence. Selection of appropriate patients for the more extensive procedure would be ideal, but at present there are no well proven selection criteria. The controversy surrounding the appropriate management of cytologically positive inguinal nodes in melanoma can be resolved only by evidence from a prospective randomized trial. At present the authors advocate CLND when the groin is heavily involved clinically, when nodes are palpable in the pelvis, when Cloquet's node is histologically positive for tumour or when pelvic CT demonstrates pelvic lymphadenopathy.

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Review

Xenotransplantation

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Background: Over the past 10 years xenotransplantation has generated much interest in the hope that it will enable us to overcome the current lack of human organ donors. This review examines the evolution and current therapeutic strategies that have been developed to overcome the predominant problem of graft rejection.

Methods: A literature review was undertaken using a Medline search from January 1966 to August 1999.

Results and conclusion: Despite the considerable advances that have been made in molecular biological techniques, xenograft rejection cannot be prevented without significant immunosuppression and toxic side-effects. The problem of delayed rejection, in particular, will probably be very difficult to overcome, although some of the difficulties associated with hyperacute rejection have been resolved. The potential risk of porcine endogenous retrovirus transmission has generated much debate recently, but it is likely that some of the important issues relating to xenotransplantation will never be resolved until carefully regulated clinical trials are allowed to begin.

Paper accepted 5 October 1999

British Journal of Surgery 1999, **86**, 1499–1514

Introduction

Xenotransplantation is the transplantation of organs or tissues between different species. During the past decade it has generated a great deal of interest, predominantly because of its potential to provide unlimited donor organs to supply rapidly growing transplant waiting lists (*Fig. 1*)[1]. Xenotransplantation should no longer be regarded simply as an experimental pursuit as it is likely to become a clinical reality in the near future. Admittedly, work must still be done to make the procedure safe and successful but, with the current lack of human organ donors, there is unlikely to be any other solution to the transplant problem. There is a particularly urgent need to expand the donor pool for patients awaiting cardiac transplantation who often die while on the waiting list.

The major barrier to clinical success has been the development of effective treatment strategies to avert the antibody–complement-dependent, hyperacute rejection (HAR) response that occurs immediately after exposure of the donor organ to a recipient's blood flow. This review outlines the evolution of xenotransplantation and discusses strategies aimed at making it a successful clinical entity.

Evolution of clinical xenotransplantation

Clinical xenotransplantation can be traced back to 1894 when an islet xenograft was performed in a 15-year-old child who received pancreatic fragments from a sheep[2]. Since then there have been a number of publications demonstrating successful xenotransplantation in animals but, for the purposes of this section, discussion will be restricted to xenotransplantation in humans.

The results of early xenotransplants, previously called heterotransplants, were very poor (*Table 1*)[3–7]. In the absence of immunosuppression, most xenografts succumbed almost immediately to graft rejection. With the introduction of the first immunosuppressive agents (azathioprine and steroids), surgeons resumed clinical xenotransplantation in the early 1960s. At that time it was assumed that appropriate immunosuppression would, in theory, allow an organ from a closely related species (a primate) to be used successfully.

In 1964 Reemstma *et al.*[8] reported a series of patients receiving kidneys from chimpanzee donors, using graft irradiation, azathioprine, actinomycin C and steroid immunosuppression. The results were better historically

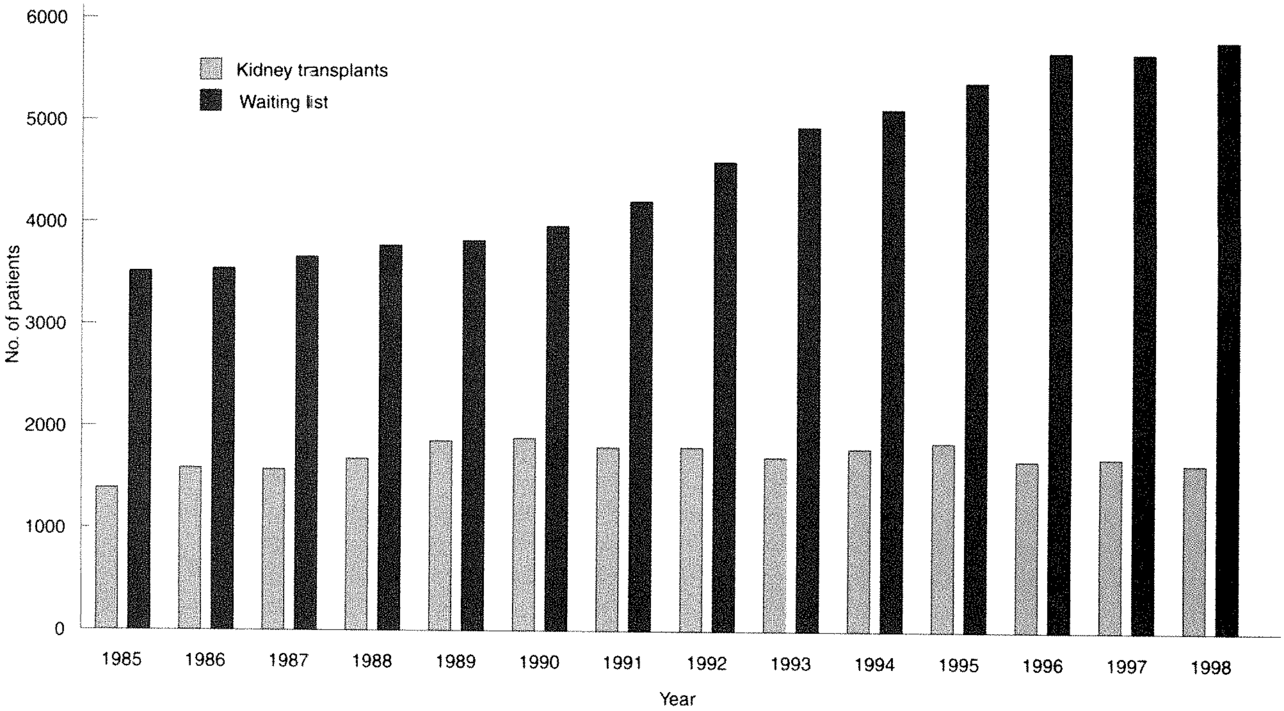

Fig. 1 Discrepancy between number of patients awaiting renal transplantation compared with the number of renal transplants performed in the UK[1]

Table 1 Xenografts before the era of immunosuppression

Reference	Year	Tissue	Donor	Outcome
Williams[2]	1894	Pancreas	Sheep	Died
Princeteau[4]	1905	Kidney	Rabbit	Died 16 days, pulmonary congestion
Jaboulay[5]	1906	Kidney	Pig	Non-functioning graft
Jaboulay[5]	1906	Kidney	Goat	Non-functioning graft
Unger[6]	1906	Kidney	Primate	Died 32 h, venous thrombosis
Neuhof[7]	1923	Kidney	Sheep	Died 9 days

but the impact was not as good as had been hoped for; the longest survival was only 9 months (*Table 2*)[8–25]. With further experience it became clear that organs from a different species could maintain life in a human recipient, but graft rejection similar to that seen after allotransplantation still occurred. At that time more success was achieved with *ex vivo* perfusion of animal livers than with xenotransplantation, suggesting a need for better immunosuppression[26]. Reports of clinical xenotransplants were sporadic during the 1970s but in 1985 a new era resumed after the Baby Fae baboon heart to human xenograft. It was assumed, because of the immunological immaturity of the neonate recipient and the use of a new immunosuppressive agent called cyclosporin, that the baboon heart xenograft would function for longer. The child survived for 20 days, succumbing to progressive xenograft rejection[21]. It was clear, despite use of the very best immunosuppressive agents available, that long-term survival could still not be achieved.

Further clinical xenografts or *ex vivo* reperfusion[23] were described by workers in Poland[24], Los Angeles[23] and Pittsburgh[22], USA, the latter group performing baboon to human liver xenografts. One such case involved a 35-year-old patient with hepatitis B and human immunodeficiency virus infection[22]. Baboon donors were preferred because of the resistance of their livers to hepatitis B infection. Immunosuppression with FK 506, prednisolone and cyclophosphamide was used and one patient survived for 70 days. The Polish experience was less encouraging; their recipient received a pig to human heart xenograft, but survived for less than 24 h[24]. Interestingly, both of the above xenografts

Table 2 Xenografts in the era of immunosuppression

Reference	Year	Tissue	Donor	No.	Survival
Reemtsma *et al.*[8]	1964	Kidney	Chimpanzee	12	< 9 months
		Kidney	Monkey	1	10 days
Hitchcock *et al.*[9]	1964	Kidney	Baboon	1	4·5 days
Starzl *et al.*[10]	1964	Kidney	Baboon	6	< 2 months
Hume[11]	1964	Kidney	Chimpanzee	1	1 day
Hardy *et al.*[12]	1964	Heart	Chimpanzee	1	Non-function
Traeger *et al.*[13]	1965	Kidney	Chimpanzee	3	2 months
Council on Scientific Affairs[14]	1985	Kidney	Chimpanzee	2	4 months
Cooley *et al.*[15]	1968	Heart	Sheep	1	Non-function
Cortesini *et al.*[16]	1969	Kidney	Chimpanzee	1	1 month
Ross[17]	1969	Heart	Pig	1	Non-function
Marion[18]	1969	Heart	Chimpanzee	1	Non-function
Starzl[19]	1989	Liver	Chimpanzee	3	< 14 days
Barnard *et al.*[20]	1977	Heart	Chimpanzee	1	4 days
		Heart	Baboon	1	Non-function
Bailey *et al.*[21]	1985	Heart	Baboon	1	20 days
Starzl *et al.*[22]	1993	Liver	Baboon	2	< 70 days
Makowka *et al.*[23]	1995	Liver	Pig	1	1 day
Czaplicki *et al.*[24]	1992	Heart	Pig	1	< 24 h
Groth *et al.*[25]	1994	Islets	Pig	10	Non-function

had little evidence of rejection. In the case of the liver xenograft, the recipient's hepatic profiles became those of the baboon with no obvious adverse effects.

The transplantation of porcine fetal islets into human insulin-dependent diabetic patients has also been attempted, both by intraportal infusion and by placement under the kidney capsule. Unfortunately, for neither method were clear increases in serum C-peptide levels demonstrated[25,27–29]. All 12 patients had received previous renal allografts with standard triple immunosuppressive therapy (cyclosporin, azathioprine and prednisolone). In the first five patients porcine C-peptide was detected in the urine; the longest duration was 289 days[30,31]. Fetal porcine neural cells have also been implanted into patients with Parkinson's disease and cell survival has been documented for at least 8 months[32].

Which organ donor?

Putting aside the immunological problems of organ rejection, a xenograft must have similar physiological and morphological characteristics to those of the recipient. In general terms the most obvious choice of animal is the large non-human primate, such as the chimpanzee. In physiological terms humans and chimpanzees have marked similarities and their genomes differ by only 3 per cent[33]. Nevertheless, chimpanzees pose logistical problems, such as near extinction, a slow rate of reproduction and other drawbacks of large-scale primate breeding. These considerations have led investigators to seek an animal donor that is phylogenetically unrelated[34].

Ethical considerations and cost effectiveness favour pigs as the species of choice. Ethical constraints are fairly restrictive, but pigs are freely slaughtered for human consumption[35] and have several advantages over other animals of comparable size. They require less space to breed, and are easy and inexpensive animals to feed compared with primates, sheep, cattle and goats[35,36]. More importantly, pigs have a high reproductive capacity, with oestrus cycles every 3–4 weeks producing large litters of up to 20 piglets which reach sexual maturity at 6 months[36]. Although porcine organs have remarkable physiological and anatomical similarities to those of humans, attention must be paid to hormone secretion, enzyme transmitters and growth factors[37]. Certainly the last might stimulate a xenogeneic donor organ to undergo uncontrolled growth in, for example, a porcine heart to human combination. Despite similarities between human and porcine albumin (65 per cent), erythropoietin (82 per cent) and complement (70 per cent), some of these elements may be non-functional in the transplant setting. Porcine erythropoietin in a primate host is a good example of this phenomenon[38].

Xenograft rejection

After investigations by Perper and Najarian[39] it was soon realized that there were distinctly different rates of rejection between phylogenetically distant donors (dog to pig) compared with closely related species (chimpanzee to human). At the time it was proposed that the presence of cytotoxic antispecies antibodies (preformed natural antibodies; PFNAs) within the recipient's circulation mediated the rapid onset of xenograft rejection after exposure to donor endothelium. Based on this, the descriptive terms 'concordant' and 'discordant' pairs were used to differentiate between xenografts with prolonged graft survival and those that were rapidly rejected[40].

There are a number of ways to prevent HAR in some discordant species combinations and HAR does not occur at all in concordant combinations. Even so, rejection still occurs 2–3 days later and this process has been described as delayed xenograft rejection (DXR), or acute or accelerated vascular rejection. The predominant difference between HAR and DXR is that the latter is a slower non-complement-dependent process (type II endothelial activation)[41]. There are many aspects of xenograft rejection that are likely to have an important influence on graft survival. It is thought that a concurrent interplay between PFNAs, complement activation and cell-mediated immunity induces xenograft rejection. These individual components will now be discussed with the discordant pig to human model in mind.

Preformed natural antibodies

The role of xenoreactive PFNAs in the pathogenesis of xenograft rejection has remained controversial for many years. The binding of human PFNAs to donor xenogeneic tissue, particularly vascular endothelium, triggers activation of the complement cascade and HAR (type I endothelial activation) within minutes, similar to that seen in ABO-incompatible allografts. Many animals have circulating antibodies that react with cells and tissues from totally unrelated species without any previous antigenic immunization. The predominant target epitope for human PFNAs on porcine organs is the α1,3-galactosyl epitope. PFNAs and their target antigens are not well characterized but immunoglobulin (Ig) M subtypes are the most abundant and most damaging during HAR[42]. Studies have shown that nearly all humans possess PFNAs against various carbohydrate antigens expressed on a number of cell types, particularly the vascular endothelium[43–46]. It is estimated that 0·1–0·2 per cent of all B lymphocytes, mainly of the CD5-positive subset, spontaneously produce them[47–49].

The origins of PFNAs are unknown but some subclasses show a preponderance of IgG_2[50]. In healthy humans this is produced in response to polysaccharide antigens. IgG_2 also commonly reacts with antigens composed of carbohydrate polymer moieties that form the backbone of bacterial cell walls[51]. It has therefore been proposed that PFNAs may represent unpredictable cross-reactivity between antibodies directed against common bacterial antigens. Indeed, human PFNAs are absent at birth but development of anti-Gal antibodies, with loss of galactosyl transferase, may represent a survival advantage by reducing interspecies transfer of pathogens. Experimental evidence favours this hypothesis in that lower concentrations of PFNAs are seen in animals raised in a gnotobiotic environment[52]. It is unlikely that their origin is from antigenic stimulation alone, merely representing a physiological development of γ-globulin[53] that provides early defence against microbes before induced responses can occur. This typical broad pattern of reactivity, low affinity and high avidity for antigen, is therefore in keeping with the IgM isotype predominance that is central to HAR[54].

PFNAs in humans have been shown to react with many 'polyreactive'[55] glycoproteins[56–58]. It is well recognized that PFNAs bind avidly to oligosaccharide determinants having a terminal galactose and alpha linkage to unfucosylated hexose (Gal α1,3-Gal)[59,60]. This epitope is the target of 75 per cent of all PFNAs. These antibodies are absent in humans and higher order primates because of a mutation in galactosyltransferase that renders it non-functional[54]. Conversely, these species use a 1,2-fucosyl transferase to form H substance. It is also important to appreciate that not all cells express Gal α1,3-Gal. For example, it is absent on dispersed pancreatic B cells but is present on other cell types within pancreatic islets[61]. It is also expressed on fetal islets[62,63].

By depleting PFNAs and overcoming complement activation, discordant vascularized xenografts can have prolonged survival, but the graft is then subject to DXR (type II endothelial activation) within the next few days. This involves a complex sequence of events during which there is increased expression of adhesion molecules, tissue factor, chemoattractant cytokines and monocyte chemoattractant[64]. DXR is characterized by progressive infiltration of the graft by monocytes and natural killer (NK) cells, platelet aggregation[65] and endothelial activation[66]. More importantly, DXR appears to be resistant to all forms of conventional immunosuppression.

Xenoantibody formation during DXR occurs independently of T lymphocytes and even in the presence of calcineurin inhibitors[67]. In this situation xenoantibodies may activate the endothelium by a process called antibody-dependent cell-mediated cytotoxicity in combination with macrophages[68] and NK cells[69], in addition to antibody-independent mechanisms. NK cells can damage and lyse xenogeneic vascular endothelium *in vitro*[70], *in vivo*[71] and after *ex vivo* organ perfusion by independently recognizing xenogeneic epitopes such as Gal α1,3-Gal[72]. Antibody-dependent NK cell cytotoxicity exerts its effects through its low-affinity Fcγ receptor enabling it to bind to the xenogeneic target cell, releasing cytokines (e.g. interferon γ, interleukin 1β) and membrane attack molecules (e.g. perforins and granzymes). Direct cytotoxicity occurs independently of antibody through interactions with major histocompatibility complex (MHC) class I molecules[73].

Complement activation

Complement components provide a potent non-specific defence against foreign xenogeneic tissue. In short, a combination of events is generated via two different pathways called 'classical' or 'alternative'. As noted above, it is thought that PFNAs bind to antigenic porcine epitopes via their Fc region, binding with C1q which activates the classical complement pathway. In contrast to the classical pathway, the alternative pathway can be activated in the absence of PFNAs[74]. This occurs through a selection of damaged tissues mostly of bacterial origin, polysaccharides and IgA or IgE[75], thus bypassing C1, C2 and C4. Evidence supporting the role of both pathways in xenograft rejection stems from studies in which PFNAs have either been blocked or reduced in concentration yet graft rejection still rapidly occurred[74]. The terminal sequence of events in both pathways results in the formation of a C5 convertase complex yielding a membrane attack complex (C5b-9) that penetrates plasma membranes causing cellular death[76]. Many by-products of the complement cascade also participate in tissue destruction by stimulating the production of potent inflammatory mediators, such as cytokines, free radicals, histamine and prostaglandins[77].

PFNAs mediate discordant HAR via the complement cascade by causing endothelial activation[57] and immunological events both *ex vivo*[78] and *in vivo*[22,79]. For example, if porcine organs are perfused with human blood there is marked vascular deposition of IgM, IgG, fibrinogen, C3, C1q, macrophages, T cells, B cells and NK cells[78,80,81]. The fact that complement activation occurs during discordant xenograft rejection is further confirmed by a precipitous decrease in serum complement by sequestration[22,79]. Moreover, the administration of complement inhibitors, such as cobra venom factor (depletes C3 and C5)[82], C1 inhibitors[80] and decay accelerating factor (DAF) (CD55, a C3 and C5 convertase inhibitor)[83], prevents HAR in some species combinations.

Exposure of endothelial cells to cytokines, e.g. tumour necrosis factor α or other inflammatory mediators, causes structural and metabolic changes. Endothelial activation results in the conversion to a procoagulant environment through the release of tissue factor and plasminogen activator inhibitor which decreases *in vivo* cell surface thrombomodulin activity[57]. Platelet adhesion ensues and there is upregulation of endothelial–leucocyte adhesion molecules[84,85]. The action of PFNAs and complement causes a receptive loss in heparan sulphate binding and anticoagulant action via antithrombin III. This series of events leads to platelet aggregation, neutrophil adhesion and fibrinogenesis, which together cause the interstitial haemorrhage, inflammation, oedema and thrombosis that characterize HAR[86,87]. Whether endothelial activation by complement is PFNA dependent in all donor–recipient combinations remains to be proven conclusively[86].

Cell-mediated xenograft rejection

In most instances cell-mediated xenograft rejection is of secondary interest because of the overwhelming damage caused by PFNAs. None the less, with increasing realization that HAR is likely to be overcome, cell-mediated rejection is assuming an increasing importance. In contrast to vascularized grafts, such as liver, pancreas and kidney[88], cellular xenogeneic grafts, such as islet, bone marrow and hepatocytes, are less susceptible to HAR. The latter grafts are rendered avascular[89,90] and so cellular rejection[91,92] is likely to be more important than HAR.

The role of cell-mediated immunity in xenograft rejection[93] is still unclear but CD4-positive T lymphocytes are predominantly responsible for the greater strength observed in xenograft rejection[21,22]. The basis of transplant recognition is the ability to recognize polymorphic residues on allogeneic MHC as 'foreign' but, in the case of a widely divergent MHC across a wide species barrier, host CD4-positive cells may not be able to make this recognition, so reducing the chance of xenospecific recognition[94,95]. Thus divergent T cell and antigen-presenting cell (APC) xenogeneic interactions may be less important than corresponding responses to allogeneic antigens[96] and, indeed, cause less of a primary proliferative response than allogeneically mediated rejection[97]. There are also likely to be differences in species-specific signals, such as cytokines, accessory molecules and co-receptor interactions, which might not be efficient stimuli for T cell activation when there is marked species disparity[93]. This may partly explain why studies of T lymphocyte recognition of discordant xenografts have produced conflicting results[98,99]. These studies are also somewhat difficult to interpret as they have been performed in non-human models and have been applied to *in vitro* mixed lymphocyte co-cultures which do not necessarily predict the same response *in vivo*.

Xenogeneic T cell–APC interactions also need to be considered in terms of direct and indirect host sensitization. During direct antigen presentation, host T cells recognize donor APCs in cooperation with xenogeneic MHC molecules. As already stated, a species-specific reaction may be of limited significance in some combinations because disparity has the potential to block functionally direct xenoantigen recognition. The response needs to be activated through all the appropriate interactions between the T cell receptor and xenogeneic MHC, in addition to interactions between accessory and co-stimulatory molecules (e.g. intercellular adhesion molecule 1 and lymphocyte function associated antigen 1). Inefficient interactions during the direct xenoresponse have been reviewed elsewhere and so will not be discussed in detail[97] but, in summary, there appears to be a high degree of homology between porcine and human MHC class II antigens[100].

A number of *in vitro* studies support the role of indirect xenoantigen presentation[101,102] by host APCs expressing processed xenoantigens in association with self MHC antigens[103]. Experimental evidence, mainly in rodent combinations, demonstrates extended survival of immunomodulated xenografts in combination with antilymphocyte serum[104,105]. Pretransplant immunomodulation using γ irradiation depletes the donor APCs necessary for direct antigen presentation but additional strategies are needed to avert the indirect response. APC-depleted murine pancreatic islet allografts are never rejected, whereas APC-depleted rat xenografts are[105]. Lacy[106] has shown the benefit of pretransplant culture in removing graft APCs, with extended survival of rat, hamster, rabbit and human islets when transplanted into murine recipients. Nevertheless, anti-CD4 monoclonal antibody was also needed for immunosuppression. A more recent study by Chitilian *et al.*[107] has confirmed these observations by documenting that MHC class II-deficient mice have prolonged survival of porcine skin grafts as a result of their inability to mount a CD4-positive T cell-mediated indirect response. The increased magnitude of the indirect response can be partly explained by the presence of a high population of pig-specific MHC class II restricted T lymphocytes that respond avidly to the numerous porcine proteins that are processed by host APCs[107,108].

It is clear that CD4-positive cells play a dominant role in xenogeneic graft rejection[109] that is different to that of allograft rejection in which rejection is predominantly through direct alloantigen recognition. CD4-positive T cells can mediate rejection independently of NK cells, B cells and CD8-positive cells. It also appears that the CD4-positive macrophage is one of the main cells infiltrating xenografts. CD4-positive T lymphoctyes seem to restrict themselves to the periphery[110]. CD8-positive lymphocytes also have a role in xenograft rejection, but this differs from that seen in the allogeneic situation. In support of this, it has also been shown that in CD8-deficient mice islet xenografts are acutely rejected, whereas allografts have prolonged survival[105,111]. CD4-positive T lymphocytes appear to mediate responses to both MHC class I[95] and MHC class II[112] xenogeneic antigens.

Taken together, these facts suggest that the cell-mediated xenogeneic response is predominantly indirect. The specificity of the effector cells that destroy the graft has still not been completely determined. In summary, responsive T cells would not be directly graft specific but specific for graft antigens in association with host MHC class II antigen. This simply means that a divergent xenograft may be weakly immunogenic, but strongly antigenic in comparison to the host, being greatly stimulatory for indirect antigen presentation[93,95]. Current methods capable of immunomodulating allogeneic grafts by inhibiting direct antigen presentation are, therefore, not appropriate for xenogeneic grafts for which cellular rejection is largely mediated by indirect antigen presentation.

Strategies for preventing xenograft rejection

For long-term xenograft survival the antiporcine T lymphocyte xenogeneic response will have to be suppressed without toxic or life threatening side-effects. A number of strategies have been proposed.

Immunosuppression

The recent American[113] and European[114] multicentre trials show that FK506 is superior to cyclosporin in preventing liver, but not renal, allograft rejection. This suggests that immunosuppression regimens need to be tailored to individual organs; this is probably going to be even more important for xenografts than allografts. Previous immunosuppressive regimens[21,23–25] used to prevent xenograft rejection have not markedly differed from those used to combat allograft rejection, simply because few other alternatives exist. Immunosuppression by steroids, azathioprine and cyclosporin has formed the backbone of most clinical regimens. Slight modifications have been made by Starzl *et al.*[22] who attempted to reduce the B cell response using cyclophosphamide. The problem here is that the therapeutic doses are considered to be too toxic. Other modalities include leflunomide, 15-deoxyspergualin (DSG) and splenectomy. Anti-B cell agents (e.g. cyclophosphamide) in conjunction with prostaglandin E_1 have been used for baboon to human liver xenografts. In this case grafts have survived for 70 days and evidence suggests that the immune response could be attenuated with combined anti-B cell and anti-T cell therapy. The most recent clinical experience has been with a cyclosporin, prednisolone and azathioprine combination used for porcine islet cell cluster xenotransplants[25], but the prevention of graft rejection was not demonstrated conclusively.

Experimental models have shown some success in preventing porcine islet discordant xenograft rejection with FK 506 both *in vivo* (pig to rat)[115] and *in vitro* (pig to human)[116]. Results with newer immunosuppressives, such as mycophenolate mofetil[117,118], are eagerly awaited because of the known diabetogenic effects of FK 506[119]. Using total lymphoid irradiation and cyclosporin for suppressing B lymphocyte activity has prolonged survival for more than 100 days compared with only 2–5 days when each of these modalities is used alone[120]. The most recent clinical experience has been with a cyclosporin, prednisolone and azathioprine combination used for porcine fetal islet cell cluster xenotransplants[25], but the prevention of graft rejection was not demonstrated conclusively.

Although the specific mode of action of DSG awaits further clarification, it is thought to elicit some alteration of thymus and T cell actions[121]. It inhibits natural antibody production in a discordant xenograft model[121,122], although not to a degree that is sufficient to prevent cell-mediated rejection[123]. Graft survival can be prolonged by DSG in combination with FK 506[124], simultaneous splenectomy[125] or antithymocyte globulin[126].

The isoxazole derivative leflunomide has potent immunosuppressive properties in xenotransplant models by blocking the calcineurin-independent pathway of T lymphocyte proliferation. It can also suppress B cell activation and xenoantibody formation both *in vitro* and *in vivo*[127,128]. More recent investigations suggest that leflunomide in combination with cyclosporin can prolong xenograft survival in a rat–hamster model by suppressing formation of T cell-independent xenoantibody of the IgM isotype[129]. This is known to be particularly important in DXR. Some immunosuppressive protocols have been directed at blocking the activation of NK cells by using combination therapies, such as rapamycin, antilymphocyte serum (ALS) and NK cell-directed monoclonal antibodies. Such combinations have been shown to prolong xenograft survival in rodent models[71]. Rapamycin, for example, can inhibit T cell proliferation as well as xenoantibody production by B cell suppression[130].

Despite the existence of various empirical combination therapies, no current drug regimen has produced an acceptable duration of xenograft survival in larger mammals. It is becoming increasingly clear that systemic immunosuppressive therapy alone will be ineffective in achieving long-term graft survival. It must also be appreciated that chronic rejection, which has been an important cause of poor long-term allograft survival, may prove to be more of a problem for xenografts where the T cell response is largely indirect. In summary, an ideal immunosuppressive regimen would have to reduce the recipient PFNA concentration, simultaneously manipulating the complement armoury and cell-mediated response *in vivo*, without being too toxic to the recipient. The future success of xenotransplantation will require highly specific combination therapies with both anti-B cell and anti-T cell activity and, ultimately, the induction of tolerance.

Preformed natural antibody suppression and depletion

Human plasma can be exchanged for substitutes such as fresh frozen plasma or human albumin solution by a technique called plasmapheresis. This treatment depletes PFNA levels, but effective reduction may require repeated exchanges over periods of weeks or months. Alexandre *et al.*[131] have applied this method in a pig to baboon renal xenograft model, prolonging xenograft survival for 22 days. Unfortunately, after plasmapheresis PFNA levels may return to higher than original levels within 24 h[132]. To combat this, other investigators have used cyclosporin, splenectomy or cyclophosphamide, as conventional immunosuppression[133] is ineffective in inducing a prolonged depletion of PFNAs.

Another useful approach is to remove PFNAs by sequestration. This can be done by *ex vivo* perfusion of porcine organs or using protein columns[134]. Immunoaffinity columns with Gal-like oligosaccharides that absorb serum and PFNAs have also been tried. After *ex vivo* perfusion another organ taken from the same donor or species can then be transplanted into a PFNA-depleted recipient[81]. This application has been predominantly experimental; attempts in a clinical setting have been made but have not succeeded in prolonging survival[24].

Transient PFNA depletion by plasmapheresis should protect the xenograft from early destruction as the rebound rise of PFNAs will not cause HAR[135] in all cases. For example, temporary depletion of antibodies in sensitized patients receiving ABO-incompatible renal allografts can sometimes lead to survival for long periods[136]. The precise mechanism of this phenomenon, which is called graft accommodation, is unknown[137]. A series of explanations have been proposed, including formation of new antibodies of a different isotype or specificity to endothelial antigens, altered or lost expression of xenoantigens, and a lack of unresponsiveness to endothelial activation[137].

In summary, the use of plasmapheresis or *ex vivo* organ perfusion to prolong xenograft survival is limited, as it not only removes PFNAs but also has a tendency to reduce non-pathogenic immunoglobulins. After repeated courses it may cause graft thrombosis, anaphylactoid reactions and transmission of viral pathogens[137,138].

Immunomodulation

Other efforts to abrogate the rejection response have included immunomodulation. The principals of immunomodulation are based on the concept that passenger leucocytes (e.g. dendritic cells) within a xenograft can stimulate rejection as they express MHC class II antigens. Pretreatment of xenografts by immunomodulation aims to delete passenger leucocytes making graft rejection less likely. Immunomodulation protocols have generally been developed for islet xenografts. Most have been used in rodent (concordant) models. Graft survival has been significantly inferior to that achieved in allograft models in both ultraviolet B-irradiated concordant[139] and discordant (primate to mouse)[140] models, again supporting a role for indirect antigen presentation. Similar results have been demonstrated with γ irradiation and ALS (rat to mice)[104].

Encapsulation

Another strategy is encapsulation of xenografts. This is again restricted to cellular grafts, such as islets of Langerhans. The prinicipal of encapsulation is that the graft should be protected from rejection by an encapsulating biocompatible membrane. O'Shea and Sun[141] were the first to demonstrate long-term survival (144 days) in a concordant (rat to mouse) islet xenograft model. Subsequently encapsulation has been proven to prolong survival (51 days) in discordant models (dog to mouse) with minimal cellular reaction[142]. Success in larger mammals has been more difficult to achieve. Encapsulation and transplantation of porcine islets into four cynomolgus monkeys has also been reported[143,144]; although porcine C-peptide was detected in all recipients only one remained insulin independent (for 360 days)[143].

It was originally thought that one of the advantages of islet encapsulation is its ability to exclude PFNAs from the xenogeneic tissue, thereby preventing HAR. More recent investigation suggests that this is immaterial, as graft survival can still be prolonged (up to 10 weeks) in a porcine islet to mouse combination when the islets are encapsulated in uncoated, PFNA-permeable, microspheres[145]. These findings suggest that when rejection occurs there is also a significant cell-mediated response[145] and that exclusion of PFNAs from islet tissue is not critical for islet xenograft survival. Most encapsulated grafts eventually succumb to pericapsular fibrosis. This can be circumvented by using anti-CD4 monoclonal antibody therapy, indicating that xenogeneic antigens escape from the capsule, stimulating an indirect rejection response and pericapsular fibrosis[146].

Genetic manipulation

The strategy that is most likely to be successful in abrogating HAR is the genetic manipulation of donor tissue which, in recent years, has generated considerable interest for those involved in xenotransplantation. With the understanding that complement is critically involved in HAR, recombinant DNA technology has been used to produce complement inhibition. Dalmasso *et al.*[83] were the first to demonstrate that isolated human DAF added to porcine endothelial cells inhibits human complement-mediated cytotoxicity *in vitro*. Attempts have since been made to engineer potential porcine donors with human complementary DNA (cDNA) for the donor DAF (CD55) or membrane cofactor protein (MCP) (CD46) genes that inhibit C3 and C5 convertases in both the classical and alternative pathways. Preliminary experiments in a mouse to human model demonstrate complement inhibition[147]. On the basis of these encouraging results, transgenic pigs have been developed that express human complement regulatory products such as DAF and MCP. There is speculation that these will serve as organ donors for human recipients in the near future. Even after elimination of HAR by averting the deposition of PFNAs and complement activation, it is likely that graft rejection will still occur as a result of the antibody response seen in concordant xenograft rejection. The hope is that it will be possible to abrogate this by anti-B cell immunosuppression.

Transgenic expression of human complement regulatory proteins in porcine donors[148] has shown extreme variation, but 67 per cent of pigs express the transgene in skin, liver, spleen, lung and heart. Primate studies have demonstrated survival of porcine hearts transgenic for human DAF (CD55) for up to 60 days without evidence of rejection. Unfortunately, high levels of immunosuppression are required and have led to adverse side-effects in the recipients[149,150].

As noted above, the 1,3-galactose epitope is the major xenoantigen expressed on porcine cells. If the α1,3-galactosyltransferase that creates this xenoantigen could be eliminated from a porcine organ, it may be possible to avert xenograft rejection. The gene encoding the expression of porcine α1,3-galactosyltransferase has been cloned[151]. This tranferase enzyme galactosylates lactobiose to produce Gal α1,3-Gal expression and it seems appropriate to negate this gene in pigs by homologous recombination. However, the technology to produce porcine embryonic stem cells has yet to be perfected and so this has only been achieved in mice. Unfortunately, although this novel idea solves one problem it also creates another; by knocking out this gene other subterminal sugars that bind PFNAs are exposed. An alternative approach known as 'transferase dominance' has been shown to induce a more favourable pathway in rodents, in that lactosamine can accept fucose in preference to galactose, under the influence of H-transferase, instead of α1,3-galactosyltransferase. This essentially reduces the expression of Gal α1,3-Gal[152], replacing it with the non-antigenic human blood group O antigen, α1,2-fucosyl lactosamine moiety (H epitope)[153], which resists PFNA binding and so reduces HAR. However, its effectiveness in reducing Gal expression is dependent on cell type[154]. The α1,2-fucosyltransferase transgenic approach is still worth pursuing, given that it is less likely to produce new epitopes capable of binding PFNAs compared with α1,3-galactosyltransferase gene inactivation by homologous recombination[155].

Finally it must be emphasized that most, but not all, human IgM PFNAs are directed at this xenoantigen[156] and so it is unlikely that HAR will be totally prevented by such highly specific targeting. However, if the severity of the response could be reduced, this advance may help to induce xenospecific tolerance during the early transplant period. A better approach would be to deplete the MHC complex from all tissues providing suitable 'blind organs' but, because of the highly polymorphic nature of MHC molecules, monoclonal antibody therapy cannot be the solution, leaving genetic manipulation as the only answer.

Immunological xenogeneic tolerance

The process of immunological tolerance (graft stabilization or graft accommodation) involves a change in the graft whereby its inherent vulnerability to rejection decreases with time[157]. By achieving immunological tolerance between recipient and graft, toxic immunosuppressives might be withdrawn. There are many experimental models of allogeneic and xenogeneic tolerance, particularly in rodents, but tolerance in humans has remained an elusive goal[158].

Current methods of achieving tolerance involve pretreatment of donor tissue by immunomodulation, immunosuppression and monoclonal antibody therapy, or recipient treatment by infusion of donor lymphoid cells derived from blood, spleen or bone marrow, with or without total body irradiation[159,160]. However, irradiation can lead to severe bone marrow aplasia without improving long-term xenograft survival[161]. There are also doubts as to whether bone marrow engraftment in a xenogeneic host will be possible, owing to limits imposed by growth factors, cytokines and the presence of PFNAs. It is thought that this situation might be improved by administering donor-specific growth factors[162], or by combining the xenograft with syngeneic marrow encoding donor-specific cDNA capable of expressing donor MHC[163]. Nevertheless, despite these experimental concepts allotolerance has still not been reproduced uniformly in large animals and limited non-specific immunosuppression is always needed[164]. With respect to a porcine to primate combination, efforts to induce tolerance by mixed chimerism after additional bone marrow transplantation have not been completely successful.

The exchange of migratory leucocytes between transplant and recipient, with consequent long-term cellular chimerism, is the basis for acceptance of all whole organ allografts and xenografts[165]. It is assumed that the bidirectional migration of lymphocytes between a transplanted organ and its recipient is crucial to tolerance induction. If a delicate balance is not achieved, graft rejection or graft *versus* host disease may occur, requiring a period of immunosuppressive treatment. Studies in Pittsburgh have shown liver allograft recipients surviving for 7–13 years without immunosuppression[166]. Y chromosomes in female recipient tissues, presumably resulting from donor cell migration, were detected. With this in mind the liver, because of its dense constituency of migratory leucocytes, has been proposed as the most 'tolerogenic' organ. Strategies to achieve similar effects in kidney, heart and islet allografts have involved perioperative infusion of lymphoreticular cells obtained from donor bone marrow or spleen[159]. However, it has not been possible to prolong islet graft survival, even in the presence of a high level of xenogeneic chimerism[167].

Chimerism has also been demonstrated after baboon to human liver xenotransplantation but, once again, graft survival was short[22]. Whether failure was due to surgical difficulties or inadequate immunosuppression is not known. Newer immunosuppressive drugs or improved techniques for abrogating rejection by PFNA elimination may allow better success in the future. Current regimens utilizing FK 506 with simultaneous cyclophosphamide, DSG and mycophenolate mofetil do not permit consistently reproducible xenograft survival[22].

Transmission of zoonoses from donor to recipient

The problem of potential disease transmission from donor to recipient and from recipient to the general population needs to be addressed. The pig can harbour many bacterial, viral, fungal and protozoal organisms. Undoubtedly, some micro-organisms could be transferred after xenotransplantation. Current laboratory procedures are not always adequate in detecting the presence or guaranteeing the absence of a virus. One way to circumvent this problem might be to use gnotobiotic animals that are reared in an environment which carries a low risk of infection[168]. However, this is so expensive and labour intensive that it seems an impractical solution.

Another dilemma is how to screen organs rapidly for infection. Both humans and non-human primates harbour not only their own viruses but may also be infected with viruses of other primate origin that only become apparent in an immunocompromised host. There are still many unclassified viruses, particularly of the simian variety. Others remain to be isolated from non-human primates and so little is known of their potential for infection or transmission[169]. The baboon is resistant to the majority of human viruses, which is not the case for the chimpanzee. Non-human primate donors substantially increase the risk of transmitting viral infections compared with porcine donors. However, certain viral pathogens are thought to be transmissible from pigs to humans, including herpes simplex type 1, varicella, cytomegalovirus and Epstein–Barr virus[170].

The threat of transmissible disease is one of the most discussed issues at present[171], especially in the Nuffield Council on Bioethics and by the UK Department of Health. This concern has been reinforced by reports of co-culture of porcine and human cell lines that allow porcine endogenous retroviruses to begin replication[172]. Retroviruses are particularly difficult to eradicate as they become a permanent part of the mammalian genome. Usually they do not replicate, but this variable event may occur in an immunosuppressed recipient. Martin *et al.*[173] have also demonstrated the release of porcine endogenous retroviruses from cultured porcine endothelial cells *in vitro*. Conversely, extensive studies of patients who have received xenografts of porcine origin[174], and have been maintained by bioartificial liver support using porcine hepatocytes or been exposed to pig kidneys by *ex vivo* perfusion[175], have not demonstrated any retrovirus transmission. Indeed a 1999 study involving 160 subjects exposed to porcine living tissue failed to demonstrate any retroviral cross-infection[176]. Similar observations have been found with porcine aortic endothelial cells transplanted to baboon recipients; porcine endothelial retrovirus transmission does not occur despite viral messenger RNA being detected in the endothelial cells. It therefore appears that transmission can occur *in vitro* but is less predictable *in vivo*[177]. Consequently, regulatory authorities in the USA and UK[178] now require that all potential tissues for xenografting are tested for the presence of porcine endogenous retroviruses. In combination with regular surveillance, it is hoped that this policy will eliminate the risk of transferring such retroviruses into the human genome.

Conclusion

Whole organ xenografting is still associated with a number of fundamental problems, the most important of which are xenograft rejection and the risk of viral transmission to recipients. The elimination of DXR and the indirect cellular xenogeneic reponse is a major problem because of the many porcine peptides that contribute to proliferation of MHC restricted T cells. The potential risks of xenotransplantation can, in the final analysis, only be understood through clinical trials.

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Original article

Training opportunities in liver transplantation surgery

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Background: Liver transplantation surgery is carried out in only a few selected centres in the UK. This study was performed with a view to identifying potential training opportunities available for the general and specialist higher surgical trainee, and also to assess the outcome following liver transplant surgery according to the grade of the surgeon performing the procedure.

Methods: Data on 111 liver transplants with caval preservation undertaken consecutively in a single unit during a 32-month period were collected and analysed. The transplant procedures were grouped into those performed by consultants and those performed by supervised trainees. Survival was estimated by the Kaplan–Meier method. The Cox regression model was used to examine the influence of grade of the surgeon on survival. χ^2 and independent sample t tests were used to identify significant preoperative, intraoperative and postoperative variables.

Results: Trainees carried out 34 recipient hepatectomies (31 per cent), 47 implant procedures (42 per cent) and all 143 retrieval operations. The mean time taken by a supervised trainee to carry out a recipient hepatectomy and implantation was 183 and 44 min compared with 165 and 46 min for a consultant ($P = 0{\cdot}22$ and $P = 0{\cdot}44$ respectively). The mean intraoperative red cell requirement was 8 units for both consultants and trainees ($P = 0{\cdot}85$). The overall patient survival rate was 88 per cent at 3 years and the grade of the surgeon made no difference to survival or the occurrence of complications ($P > 0{\cdot}05$).

Conclusion: The outcome following liver transplantation with caval preservation did not differ according to the grade of the surgeon performing the procedure. Extensive training opportunities are available to learn hepatobiliary and vascular surgical techniques in liver transplantation surgery.

Paper accepted 5 August 1999

British Journal of Surgery 1999, 86, 1515–1520

Introduction

Liver transplantation in the UK is currently carried out in only seven designated centres[1]. In many of these centres, liver transplantation surgery is closely allied with hepatobiliary and pancreatic surgery. The Specialist Accreditation Committee has identified areas in which the higher surgical trainee in general surgery with a subspecialty interest in transplantation needs to be competent at the end of training[2]. In liver transplantation, the recommended subspecialty training includes organ retrieval procedures and the advanced module includes Roux loop construction, recipient hepatectomy and liver transplantation (implant)[2]. A surgical trainee with an upper gastrointestinal interest is also expected to be familiar with or have assisted in liver transplantation[2]. However, opportunities are limited even though over 600 liver transplants and a similar number of multiple-organ retrieval operations are performed in the UK every year[1]. Potential training opportunities therefore exist in areas such as liver retrieval, recipient hepatectomy and implantation.

Approximately 50 liver transplant procedures are undertaken annually in this centre[1] in addition to the full range of hepatobiliary and pancreatic operations. The training opportunities offered in this unit between October 1995 and May 1998 were therefore examined, and the influence of the experience of the surgeon on the outcome was assessed.

Patients and methods

Data were collected prospectively for 111 consecutive orthotopic liver transplants carried out between October 1995 and May 1998 using a caval preservation ('piggyback') technique. This procedure was analysed because it affords greater training opportunities during recipient hepatectomy. The piggyback technique employed in this study was similar to that described by Belghiti *et al.* in 1992[3], the only notable exception being an end-to-end anastomosis between the donor suprahepatic cava and the common confluence of the recipient left and middle hepatic veins. The caval preservation manoeuvre was similar to that undertaken with classical hepatic resections[4]. A temporary end-to-side portacaval shunt was fashioned if there was haemodynamic upset (refractory hypotension) on trial clamping of the portal pedicle and where significant bleeding related to portal hypertension occurred, thereby making initial dissection difficult. Initial reperfusion was carried out through the portal vein or hepatic artery according to the surgeon's preference, taking into consideration anatomical factors such as size and the number of vessels involved.

Details regarding the surgeon undertaking the organ retrieval, the recipient hepatectomy and the implant procedure were collected. Trainee surgeons consisted of career and visiting registrars attached to the unit for the purpose of training at specialist registrar year 4 and above. A supervised trainee procedure was defined as one in which the trainee performed the entire procedure without the consultant having to undertake any part of the particular procedure, either recipient hepatectomy or implantation. A consultant was scrubbed for all liver transplant operations. It was considered unethical to randomize patients to consultant or trainee procedures and hence the decision as to who performed the operation was taken by the consultant, taking into consideration perceived difficulties. Trainees were not specifically designated to one of the four consultants who were equally willing to assist the trainees. Demographic details and the intraoperative findings were recorded. The various operation times involved in the liver transplant procedure were noted. Data on intraoperative transfusional requirements and postoperative complications were recorded on the database.

Patients were regarded as having fulminant hepatic failure and were listed as superurgent cases if they satisfied the King's College Hospital criteria[5]. Ascites was recorded as being present if more than 1 litre was drained during operation. Portal hypertension was deemed to be present when marked engorgement of intra-abdominal varices was noted at operation. Similarly, the presence of adhesions requiring additional dissection was also noted at operation. Time from making the skin incision to skin closure was recorded as the total operating time. Hepatectomy time was defined as the time from making the skin incision to removal of the recipient liver. Implantation included caval, portal, hepatic arterial and biliary anastomoses. Reperfusion time or secondary warm ischaemic time was defined as the time between taking the donor liver out of iced saline and reperfusion. Time from the donor cross-clamp to taking the liver out of ice at the recipient operation was termed the cold ischaemic time. The red cell concentrate, fresh frozen plasma, platelet and cryoprecipitate requirements were defined as the number of units of these blood products transfused at operation.

Intraoperative cardiac arrest was defined as cardiac arrest requiring external or internal cardiac massage. Hepatic artery thrombosis was defined as occlusion of the hepatic artery as demonstrated by both duplex scanning and angiography. Reoperations included all operations performed during the postoperative period excluding retransplant procedures. Postoperative haemorrhage was defined as clinical evidence of bleeding requiring 2 units or more of red cell transfusion. Postoperative hepatic venous obstruction was deemed to be present if demonstrated by duplex scanning and requiring radiological intervention for symptoms. All postoperative biliary complications including bile leaks and strictures were recorded. Intra-abdominal collections were defined as those demonstrated on ultrasonography or computing tomography which required radiological or surgical intervention. Primary non-function of the liver was based on the requirement for retransplant within 5 days of transplantation. Refractory ascites was defined as postoperative drainage of more than 1 litre of ascites for more than 5 days and requiring medical therapy. All culture-proven viral, bacterial and fungal infections requiring therapy were recorded. Postoperative renal failure was diagnosed in patients requiring renal replacement therapy for the first time during the postoperative period. Respiratory failure was diagnosed if the patient required ventilation for more than 48 h after operation or needed to be reventilated within 7 days of extubation.

Statistical analysis

Survival was estimated by the Kaplan–Meier method. The Cox regression model was used to determine the influence of the surgeon on survival. χ^2 and independent sample t tests were used to identify significant differences between the consultant and trainee operations with regard to preoperative, intraoperative and postoperative variables. $P < 0.05$ was considered significant.

Results

A total of eight higher surgical trainees was evaluated during the study period. All trainees had a minimum of 7 years' postregistration experience. Their involvement in the various procedures is summarized in *Table 1*. Supervised trainees carried out 34 (31 per cent) of the recipient hepatectomies and 47 (42 per cent) of the implant procedures.

Preoperative and intraoperative details of the patients according to the surgeon performing the procedure are given in *Table 2*. The groups were comparable except that the trainees implanted the liver in more patients with ascites and intra-abdominal varices. There was no difference in the operation times between the consultant and trainee procedures except for a significant increase in the cold ischaemic time when trainees performed the implant procedure (*Table 3*). The mean intraoperative transfusional requirements are summarized in *Table 4*. Overall, nine transplants did not require red cell transfusion, of which two were carried out by supervised trainees.

Table 1 Experience of surgical trainees during multiple-organ retrievals and orthotopic liver transplants

		Hepatectomies		Liver implants	
Trainee	Total no. of retrievals	Performed	Assisted	Performed	Assisted
A	9	1	1	2	1
B	21	9	1	9	0
C	17	1	10	7	5
D	46	17	32	16	35
E	11	0	5	0	5
F	27	5	14	11	8
G	6	1	2	2	3
H	6	0	3	0	3
Total	143	34	68	47	60

The 30-day mortality rate was 9 per cent and the overall predicted patient survival rate at 3 years was 88 per cent. The grade of the surgeon performing the transplant procedures was found not to be a significant variable influencing survival ($P > 0{\cdot}05$). Postoperative complications were not influenced by the grade of the surgeon performing the hepatectomy and implantation (*Table 5*).

Discussion

The piggyback procedure in liver transplantation gives excellent opportunities to learn the basic techniques of

Table 2 Patient details according to grade of the surgeon performing the recipient hepatectomy and implant procedure during liver transplantation

	Hepatectomy surgeon			Implant surgeon		
	Consultant (*n*=77)	Trainee (*n*=34)	*P**	Consultant (*n*=64)	Trainee (*n*=47)	*P**
Mean age (years)	48	44	0·12	47	47	0·75
Sex ratio (M : F)	26 : 51	14 : 20	0·45	24 : 40	16 : 31	0·70
Operation type (%)			0·74			0·05
Elective	79	77		74	87	
Urgent	21	24		28	13	
Previous TIPSS (%)	9	3	0·43	6	9	0·64
Ascites (%)	42	50	0·40	36	55	0·04
Varices (%)	40	44	0·70	30	57	0·003
Ascites and varices (%)	26	21	0·54	13	40	0·0007
Adhesions (%)	40	27	0·16	39	32	0·43
Temporary portacaval shunt (%)	61	68	0·50	69	55	0·14

TIPSS, transjugular intrahepatic portasystemic shunt. *χ^2 test

Table 3 Procedure times of liver transplant operation according to grade of the operating surgeon

	Hepatectomy surgeon			Implant surgeon		
	Consultant (*n*=77)	Trainee (*n*=34)	*P**	Consultant (*n*=64)	Trainee (*n*=47)	*P**
Total operation time (min)	354	374	0·24	353	369	0·32
Hepatectomy time (min)	165	183	0·22	n.a.	n.a.	n.a.
Reperfusion time (min)	n.a.	n.a.	n.a.	46	44	0·44
Cold ischaemic time (min)	617	607	0·77	585	653	0·04
Venacaval anastomosis time (min)	n.a.	n.a.	n.a.	16	16	0·53
Portal vein anastomosis time (min)	n.a.	n.a.	n.a.	14	12	0·28
Hepatic artery anastomosis time (min)	n.a.	n.a.	n.a.	25	22	0·25

Values are mean. n.a., Not applicable. *Independent sample *t* test

Table 4 Transfusion requirements during liver transplantation in relation to grade of the operating surgeon

	Hepatectomy surgeon			Implant surgeon		
	Consultant ($n=77$)	Trainee ($n=34$)	P*	Consultant ($n=64$)	Trainee ($n=47$)	P*
Red cell concentrate (0–40) (units)	8	8	0·85	8	7	0·41
Fresh frozen plasma (0–24) (units)	5	6	0·31	6	5	0·19
Platelets (0–18) (units)	3	2	0·58	3	3	0·99
Cryoprecipitate (0–10) (units)	1	0	0·02	1	0	0·03

Values in parentheses are ranges. *Independent sample t test

Table 5 Complications following liver transplantation according to grade of the surgeon performing the procedure

	Hepatectomy surgeon			Implant surgeon		
	Consultant ($n=77$)	Trainee ($n=34$)	P	Consultant ($n=64$)	Trainee ($n=47$)	P
Intraoperative cardiac arrest (%)	1	6	0·22	3	2	0·61
Primary non-function (%)	7	0	0·32	6	2	0·39
Hepatic artery thrombosis (%)	7	0	0·32	8	0	0·07
Haemorrhage (%)	12	12	0·99	9	15	0·37
Reoperations (%)	16	9	0·34	14	13	0·84
Intra-abdominal collection (%)	10	6	0·44	8	11	0·60
Biliary complications (%)	7	9	0·66	8	6	0·77
Hepatic venous obstruction (%)	4	3	0·64	3	4	0·75
Refractory ascites (%)	8	6	0·53	9	4	0·46
Respiratory failure (%)	12	9	0·65	16	4	0·05
Renal failure (%)	17	18	0·92	20	13	0·29
Infections (%)	48	47	0·92	50	45	0·57

hepatic surgery. The trainees gain progressive experience through retrieval operations and by assisting in the recipient procedures. Donor operations are supervised by consultants until the new trainee is considered competent to retrieve independently. Further experience is gained by undertaking the individual anastomosis during implant, through to the recipient hepatectomy with preservation of the inferior vena cava. It is evident that individual trainees performed a variable number of procedures, which is likely to be dependent on the time each trainee spent in the unit, their previous experience and their eventual career intentions. Any procedure that involved two consultants was considered to have been a consultant-led procedure although every operation provides training opportunities for a specific component of the operation. The fact that none of the 111 piggyback procedures, which represent the total experience of the unit during this time period, required interruption to the caval blood flow or conversion to venovenous bypass reflects the competence with which the surgeons undertook the recipient caval dissection and preservation.

The patient and intraoperative details were well matched for the consultant- and trainee-operated groups, except for the presence of ascites and intra-abdominal varices. Similarly the transfusional requirements were distributed equally in both the groups. Although it seems likely that consultants will operate on potentially more difficult cases, it is encouraging to note that two of the nine transplants that did not require red cell transfusion were carried out by supervised trainees. The mean cold ischaemic time was significantly greater in transplants in which the trainee performed the implant, but was still well within accepted standards. This may be related to other factors, since the mean time taken by the trainees to perform the implant procedure and to carry out the individual anastomosis was less than that for consultant staff. The mean operating times for consultants and trainees are well within the limits of those published in the literature[6,7]. It is gratifying to note that there were no significant differences in survival or the occurrence of postoperative complications regardless of the grade of the surgeon performing the transplant procedure, although it is accepted that all the trainee operations were carried out under supervision. These results are similar to those obtained for major upper gastrointestinal, hepatobiliary and pancreatic resections[8,9].

It has been argued that centres with a greater proportion of patients with modified Child grade C cirrhosis who have had extensive previous upper abdominal surgery would not be able to offer similar training opportunities. The distribution of patients with Child grade C disease was similar in the two groups and with regard to the presence of adhesions from previous surgery. The presence of a transjugular intrahepatic portasystemic shunt may minimize the difficulties of the hepatectomy and these additional risk factors would not necessarily be seen as a contraindication to a trainee undertaking the transplant procedure. It is evident that supervised training opportunities can be provided at a subspecialty level by motivated consultant staff, without compromising patient care and resources.

There is some debate in liver transplant training as to whether liver transplant surgeons should have a background in hepatobiliary surgery or renal transplantation. Consultants with a hepatobiliary background may have an advantage in having a detailed understanding of the local anatomy, biliary surgery and techniques of reduced or split liver transplantation. However, consultants trained in renal transplantation often bring with them vascular surgical expertise and a broader understanding of immunology. Ideally, training should be structured in such a way to allow the trainees interested in liver transplantation to gain experience in hepatobiliary procedures. In the present study, two surgeons had a background of hepatobiliary surgery and the remaining two were trained primarily in renal transplantation and vascular surgery.

Trainees interested in liver transplantation could be appointed to the transplant unit during their fifth and sixth year of higher surgical training. However, it would be ideal for these trainees to have obtained either hepatobiliary or vascular surgical experience during the first 4 years. All eight trainees had this level of experience when they took part in the study. Based on the number of liver transplant procedures undertaken in the UK there is the potential for ten to 15 higher surgical training posts within established transplant programmes. In the current climate, where few higher surgical trainees are committed to a career in transplantation[10,11], it is accepted that these posts may be underutilized by trainees interested in other subspecialties.

Clearly the training potential afforded by transplantation is considerable. Retroperitoneal anatomy and dissection are never more apparent than during retrieval operations and the transplantation procedure affords excellent training opportunities in retroperitoneal dissection, portal dissection and vascular anastomotic techniques. These would benefit surgeons intending to gain experience in D_2 gastrectomies, hepatectomies, pancreatectomies, suprarenal aortic surgery and trauma surgery. Every liver transplant procedure involves a cholecystectomy and a biliary anastomosis, and this experience would be advantageous to the general surgical trainee without any subspecialty interest. Similarly, the intraoperative and perioperative care in liver transplantation surgery gives the trainee a better understanding of intensive and high-dependency care as well as the rehabilitation of seriously ill patients.

In conclusion, involvement of surgical trainees does not appear to influence the outcome in liver transplantation, provided that trainees are properly supervised. There are extensive opportunities to acquire advanced surgical skills in liver transplantation surgery. This potential needs to be realized if subspecialty training is to be completed within the required time framework.

Acknowledgements

The authors thank Miss Kirsty Martin, Mrs Molly Stewart and Lothian Surgical Audit for help in collecting the data and Mr K. K. Singh for providing statistical analysis.

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Original article

Emergency cholecystostomy and subsequent cholecystectomy for acute gallstone cholecystitis in the elderly

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Background: The morbidity and mortality rates associated with acute cholecystitis are higher in the elderly. This study reports the results of treatment of acute cholecystitis in the elderly with emergency ultrasonographically guided percutaneous cholecystostomy followed by elective cholecystectomy after endoscopic treatment of any common bile duct stones diagnosed by percutaneous cholangiography.

Methods: From January 1989 to December 1998, 92 patients aged over 70 years were treated for acute gallstone cholecystitis. A group of 84 patients with ultrasonographic signs of severe cholecystitis or an American Society of Anesthesiologists score of II to IV were submitted to ultrasonographically guided percutaneous cholecystostomy. Transcatheter cholangiography was performed in all patients and endoscopic sphincterotomy was performed before operation in patients with common bile duct stones. After resolution of the acute phase and treatment of any associated diseases, patients were submitted to cholecystectomy.

Results: Cholecystostomy was performed successfully in 83 patients and permitted resolution of the acute attack in all after a mean period of 1·8 days. Cholangiography yielded a diagnosis of non-gallstone obstruction in one patient and common bile duct stones in 19 patients; preoperative endoscopic sphincterotomy and stone extraction was performed in 18 patients. Elective cholecystectomy was then performed in 70 patients with no deaths and a morbidity rate of 24 per cent.

Conclusion: Combining emergency ultrasonographically guided percutaneous cholecystostomy, preoperative endoscopic treatment of common bile duct stones and subsequent elective cholecystectomy constitutes an optimal treatment regimen for acute gallstone cholecystitis in selected elderly patients with a mortality rate of zero in the authors' experience.

Paper accepted 14 July 1999

British Journal of Surgery 1999, 86, 1521–1525

Introduction

Acute cholecystitis is one of the most frequent causes of admissions to surgical departments in Western countries[1]. The increased incidence of biliary lithiasis with increased age (13–50 per cent above the age of 70 years and 38–53 per cent above the age of 80 years) and the rise in the mean individual lifespan are the main reasons why 50–70 per cent of cases of acute cholecystitis occur in elderly patients[2,3].

The treatment is still a matter of debate. In patients not undergoing emergency surgery, the risk of perforation of the gallbladder (3–18 per cent of cases in patients of all ages with an incidence of approximately 40–77 per cent in elderly patients with severe cholecystitis) leads to an increase in mortality rate which is related both directly to the septic biliary disease and indirectly to associated diseases (i.e. myocardial infarction)[4,5]. The mortality rate after emergency surgery (performed within 48 h of the acute attack) is reported as being from 2·3 up to 19 per cent in elderly very high-risk patients[1,6–11]. These results are related to the patient's condition, the severity of cholecystitis and surgical exploration of the common bile duct in cases of intraoperative findings of common bile duct stones[12].

Since the first ultrasonographically guided percutaneous cholecystostomy performed by Radder in 1980 for the drainage of gallbladder empyema[13], several other studies in the literature have confirmed the efficacy of this procedure[1,14–19].

This study reports experience with the definitive treatment of acute cholecystitis in patients aged over 70 years, consisting of emergency ultrasonographically guided percutaneous cholecystostomy followed by elective cholecystectomy after endoscopic treatment of any common bile duct stones diagnosed by preoperative percutaneous cholangiography.

Patients and methods

From January 1989 to December 1998, 201 patients were treated for acute cholecystitis diagnosed on the basis of the clinical picture, laboratory tests and abdominal ultrasonography. Ninety-two of these patients were aged 70 years or more.

Patients with ultrasonographic signs of severe cholecystitis (a hypoechogenic band in the gallbladder wall and/or a pericholecystic fluid collection and/or thickening of the gallbladder wall to 8 mm or more) or with an American Society of Anesthesiologists (ASA) score of II to IV were included in the emergency cholecystostomy treatment regimen. Patients with mild ultrasonographic signs of cholecystitis and with an ASA score of I would have been excluded but no patients over 70 years old were encountered. Patients with generalized peritonitis for which urgent surgical treatment was indicated (six patients aged over 70 years) were also excluded. Two other patients aged over 70 years were excluded because of failure to achieve an ultrasonographic diagnosis; in these two patients the evolution of the clinical picture prompted an exploratory laparotomy which revealed the presence of acute cholecystitis.

The study group therefore consisted of 84 patients aged over 70 years (46 men and 38 women), whose mean age was 81 (range 70–98) years; there were 30 patients in the 70–75-years age bracket, 29 patients in the 75–80-years age group and 25 patients aged over 80 years.

One or more systemic diseases were associated with cholecystitis in 65 patients, 41 of whom had cardiovascular disorders. Severe cholecystitis based on ultrasonographic examination occurred in 19 otherwise healthy patients (*Table 1*).

Table 1 American Society of Anesthesiologists and New York Heart Association scores

	ASA score				NYHA score		
Age (years)	I	II	III	IV	I	II	III
70–75	12	9	8	1	13	6	0
75–80	5	13	8	3	6	2	2
>80	2	6	9	8	1	8	3
Total	19	28	25	12	20	16	5

ASA, American Society of Anesthesiologists; NYHA, New York Heart Association

All patients received antibiotics and were submitted to emergency percutaneous cholecystostomy using the Seldinger technique under ultrasonographic and radioscopic guidance. As described in a previous report[19], a transhepatic route was always used; a 7–8-Fr pigtail catheter was positioned in the gallbladder and allowed to drain under gravity.

Transcatheter percutaneous cholangiography was performed in all patients at 48–72 h. In patients with common bile duct stones, endoscopic retrograde cholangiopancreatography (ERCP) was performed to confirm the diagnosis together with treatment by endoscopic sphincterotomy plus stone extraction, where appropriate.

Following resolution of the acute attack and medical treatment of any diseases associated with the cholecystitis, patients were evaluated for cholecystectomy. Since 1992 this operation has been performed laparoscopically.

Results

At entry all patients presented with continuous pain localized in the epigastric and/or right hypochondriac region, and nausea and/or vomiting. Hyperpyrexia was present in 34 patients with a mean value of 38·3°C, clinically evident jaundice in 15 patients, and leucocytosis in 75 patients with a mean value of $15{\cdot}6 \times 10^9$ per litre.

Cholecystostomy was performed successfully in 83 of 84 patients. Failure at the first attempt occurred in three patients owing to displacement of the guidewire during introduction of the catheter with malplacement of the latter as a result. In two of these patients the cholecystostomy was repeated successfully 24 h later, whereas in one cholecystectomy was performed owing to the patient's refusal to undergo a second attempt. In two patients displacement of the catheter occurred within the first 24 h and the catheter was successfully repositioned in both. In one patient the displacement occurred after 48 h and, in the absence of clinical signs of acute cholecystitis, laparoscopic cholecystectomy was performed.

No episodes of vagal crisis occurred but a peripheral bile duct injury with transient bile leakage occurred in one patient. An intracholecystitic haemorrhage occurred in another patient with a factor VII deficiency that was not revealed by routine coagulation screening. This latter patient required urgent cholecystectomy and intensive medical treatment of the coagulative disorder because of blood loss. Twenty-eight patients complained of pain radiating to the right shoulder, which was relieved with routine analgesic drugs, and 14 patients experienced rigors during or immediately after the procedure.

After cholecystostomy the clinical symptoms of the acute attack resolved in all patients, with disappearance of spontaneous pain and fever, and reversion of serum leucocyte values to normal after a mean period of 1·8 (range 1–4) days.

Transcatheter cholangiography revealed persistence of a stone wedged in the infundibulum in 15 of 81 patients, with failure to obtain an image of the main bile duct in four patients. The common bile duct was then examined in 77 patients; stones were found in 19 and a non-gallstone obstruction in one patient with an adenocarcinoma of the papilla. Clearance of the common bile duct was achieved by means of endoscopic treatment in 18 patients and by surgery in one.

Routine microbiological samples were obtained in 70 patients, with positive findings in 61 per cent. The infections were caused by a single pathogen in 58 per cent of patients, the most frequent isolate being *Escherichia coli*.

After cholecystostomy the mean duration of drainage was 5·4 (range 2–21) days. The catheter was removed at the time of cholecystectomy in 42 patients and some days before in 28 patients for whom a delayed cholecystectomy was needed for the treatment of associated disease. The mean interval before cholecystectomy required for medical treatment of the associated diseases was 9·2 (range 2–60) days. Seventy of 82 patients were operated on, 56 during the same hospitalization and 14 during a second one. The laparoscopic approach for acute cholecystitis was introduced in 1992; before this time 24 patients were submitted to laparotomy–cholecystectomy. Since 1992, 42 patients have been submitted to laparoscopic cholecystectomy with ten conversions and four patients with severe cardiovascular disorder have been submitted to laparotomy–cholecystectomy. Intraoperative cholangiography, performed in patients in whom the common bile duct could not be studied before operation, was negative in all patients. There were no deaths and no major complications. The postoperative morbidity rate was 24 per cent; it was higher in the group of 38 patients who underwent laparotomy than in the 32 patients who had a laparoscopic procedure, although this was not statistically significant (χ^2 test).

The mean postoperative hospital stay was 5·1 (range 2–14) days and the mean overall period of hospitalization necessary for cholecystostomy, treatment of associated diseases and cholecystectomy was 9·7 (range 4–16) days, reduced in the group of patients operated on laparoscopically to 3·1 (range 2–7) and 8·1 (range 4–14) days respectively.

Twelve patients were not submitted to cholecystectomy, two owing to their very advanced age, two because of refusal of patients themselves and close relatives, and eight who were suffering from severe chronic diseases.

In the group of ten patients submitted to surgical treatment who did not undergo or had failed cholecystostomy, there were no deaths and no common bile duct stones at intraoperative cholangiography, but five patients had complications.

Discussion

The mortality rates reported for the treatment of acute cholecystitis are on average higher in elderly patients. In a study of 664 patients, Reiss and Deutsch[3] reported a mortality rate of 2·8 per cent in patients of all ages, 7·8 per cent in patients aged over 70 years and 11·4 per cent in patients aged over 80 years. Comparison and analysis of the data in study samples related to operative risk, such as patient condition and severity of cholecystitis, are hindered by the different criteria adopted in selecting patients for surgery[1,3–5,7–9,11].

Ultrasonographically guided percutaneous cholecystostomy is easy to perform and minimally invasive. In the literature, the failure rate of the procedure is reported as 0–6 per cent and the incidence of catheter displacement as 5–18 per cent. The incidence of related complications ranges from 0 to 25 per cent, but when cholecystostomy is performed under ultrasonographic guidance severe complications are rare[14,16–18]. The catheter drainage makes it possible to eliminate the risk of perforation of the gallbladder and resolve the clinical picture of acute cholecystitis with a reduction in the associated mortality rate. The results in this series are comparable to those in the literature, with resolution of the clinical picture of acute cholecystitis in all patients after a mean of 1·8 days[14–19]. Coagulative disorders are a contraindication to percutaneous procedures, as confirmed by a patient in the present series with intracholecystitic haemorrhage due to an unknown factor VII deficiency.

In patients at very high operative risk cholecystostomy may be adopted as definitive treatment. Delattre *et al.*[14] reported a series of 32 patients at high operative risk treated by percutaneous cholecystostomy with one death from myocardial infarction.

Percutaneous cholangiography performed at 48–72 h, after reduction of the oedema, gives an image of the biliary tree in most cases; in the present study it revealed persistence of a stone wedged in the infundibulum in 19 per cent of patients. This latter phenomenon was reported by Delattre *et al.*[14] in 20 per cent (of 32 patients) 3 days after drainage.

In cases of presumed choledocholithiasis, transcatheter cholangiography enables the number of diagnostic ERCPs to be reduced because, according to Graham *et al.*[20], only one-third of patients with pathological ultrasonographic appearances or abnormal liver function indices prove to have common bile duct stones. In the presence of proven common duct stones, it enables the patient to be submitted to minimally invasive treatment by endoscopic sphincterotomy plus stone extraction before operation with a feasibility rate of 85–98 per cent[21–23]. Kunin *et al.*[1] reported a 19 per cent incidence of common bile duct stones in 150 patients over the age of 65 years with a 29 per cent increase in patients aged over 80 years. The corresponding incidence in the present study was 22 per cent (19 of 84 patients) with a 32 per cent increase in those aged over 80 years.

Percutaneous cholecystostomy therefore allows adequate resolution of the acute phase of cholecystitis and any associated diseases and also endoscopic clearance of common bile duct stones; patients are thus submitted to definitive elective surgery in the best possible condition.

Not all surgeons share such general enthusiasm for the laparoscopic approach in the elderly[24–26]. The results reported, however, refer to selected patients operated on laparoscopically, with a mortality rate of 0–4·5 per cent and a morbidity rate of 21–26·7 per cent in specific geriatric series[25,27,28]. As noted by Lucidarme *et al.*[25], when data from unselected patients are considered, the mortality rate rises from 4·5 to 9·4 per cent. Emergency laparoscopic cholecystectomy without previous cholecystostomy may be a promising procedure, but it is not known to what extent the laparoscopic approach may reduce the surgical risk factors mainly correlated in the elderly to co-morbid conditions and the presence of common bile duct stones[24].

In this study the operative risks related to co-morbid conditions were evaluated with the ASA and New York Heart Association score; the incidence of high-risk patients (ASA III or IV) was 53 per cent, comparable to that of other reports[24,25]. Emergency cholecystostomy made it possible to submit 70 of 92 patients to definitive treatment by elective surgery with no deaths and an overall postoperative morbidity rate of 24 per cent. These data confirm other reports on the use of emergency cholecystostomy before cholecystectomy when possible[29,30]. The present results over the past 6 years are even more impressive, since 90 per cent of the cholecystectomies were performed laparoscopically with a morbidity rate of 16 per cent, lower than that reported in laparoscopic series[25,27,28].

Only patients with generalized peritonitis, failed cholecystostomy and a misleading diagnosis of acute cholecystitis were excluded from the authors' therapeutic regimen. This approach reduced the number of patients operated on by emergency cholecystectomy with an overall mortality rate of zero and a low morbidity rate in elderly patients suffering from acute cholecystitis.

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Original article

Gallbladder ascariasis: presentation and management

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Background: As many as 1·5 billion people around the world harbour *Ascaris lumbricoides* in the digestive tract. Gallbladder ascariasis, although less common than bile duct ascariasis, is quite often seen in endemic areas.

Methods: Some 1300 patients with hepatobiliary ascariasis, admitted between October 1992 and June 1998, were analysed prospectively. The clinical features and outcome of 56 cases of gallbladder ascariasis are presented.

Results: Forty-seven patients were diagnosed by ultrasonography and nine were diagnosed at laparotomy. Only ten patients diagnosed by ultrasonography expelled the worms spontaneously, with resolution of symptoms and signs. The remaining 37 patients underwent cholecystectomy.

Conclusion: Gallbladder ascariasis is a significant entity in endemic areas which usually requires cholecystectomy.

Paper accepted 17 July 1999

British Journal of Surgery 1999, **86**, 1526–1527

Introduction

As many as 1·5 billion people around the world harbour *Ascaris lumbricoides* in the digestive tract[1]. From the intestines, worms can invade the bile ducts causing cholangitis, the pancreatic duct causing pancreatitis, and the gallbladder causing acalculus cholecystitis or even liver abscess[2]. Gallbladder ascariasis, although less common than bile duct ascariasis, is quite often seen in endemic areas. The clinical features and outcome of 56 cases of gallbladder ascariasis are presented with emphasis on the frequent need for surgical intervention.

Patients and methods

Some 1300 patients with hepatobiliary ascariasis admitted to this institution between October 1992 and June 1998 were analysed prospectively. Patients with isolated gallbladder ascariasis formed the study group. Patients were diagnosed either by ultrasonography or at laparotomy. Those patients diagnosed by ultrasonography were treated with intravenous fluids, broad-spectrum antibiotics and antispasmodics. Serial ultrasonographic examination, full blood count and liver function tests were done every third or fourth day. Patients underwent laparotomy if they failed to expel the worms spontaneously from the gallbladder within 7–10 days or if clinical deterioration was apparent (worsening pain, rising fever, leucocytosis), the gallbladder increased in size or a pericholecystic collection developed.

Results

Isolated gallbladder ascariasis was diagnosed in 56 patients, including 17 men, 34 women (three pregnant) and five children. Forty-seven patients were diagnosed by ultrasonography and nine were diagnosed at laparotomy. The clinical features included pain in the right hypochondrium in all 56 patients; fever in 50 (89 per cent); tenderness in the right hypochondrium with a gallbladder mass in 45 (80 per cent); vomiting in 30 (54 per cent); vomiting of worms in 25 (45 per cent); pain radiating to the back and right shoulder in ten (18 per cent); and jaundice in ten (18 per cent). Some 35 patients (63 per cent) had leucocytosis and 12 (21 per cent) had a minimal increase in bilirubin level.

In 47 patients diagnosed by ultrasonography the findings were as follows: a distended and thick walled gallbladder in 30 patients; a long coiled echogenic structure in the gallbladder in 15 (*Fig. 1*); an echogenic structure that exhibited zigzag movements suggestive of live worms in 11; a tubular echogenic strip within the gallbladder lumen in ten; an echogenic structure extending across the lumen giving a septate appearance in seven; a tubular coiled echogenic structure in the cystic duct in four; a distended gallbladder with sludge in five; and a pericholecystic collection in three patients.

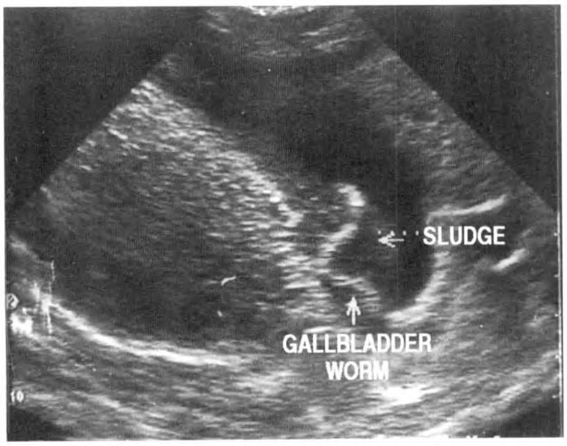

Fig. 1 Biliary ultrasonograph showing *Ascaris lumbricoides* as a coiled echogenic structure within a gallbladder containing sludge

The nine patients diagnosed at laparotomy had clinical features of acute cholecystitis but no worms were demonstrated at preoperative ultrasonography. At laparotomy, five patients had an empyema, one had a mucocele, one a distended gallbladder and two had gallstones with a distended gallbladder. All nine patients underwent cholecystectomy and were found to have dead, macerated worms in the gallbladder. Two of the five patients who had empyema developed sepsis and died after operation.

Only ten of the 47 patients diagnosed by ultrasonography expelled the worms spontaneously, with resolution of symptoms and signs. In the remaining 37 patients the clinical signs persisted or worsened and these patients underwent cholecystectomy.

Discussion

Ultrasonography has made the diagnosis of gallbladder ascariasis possible without operation, yet a significant number of patients with gallbladder ascariasis are still missed at ultrasonography especially if the worms are dead or the gallbladder contains stones. In this study ultrasonography identified gallbladder ascariasis in 47 cases (84 per cent) and missed the diagnosis in nine (16 per cent). Khuroo *et al.*[3] in 1992 reported 13 cases of gallbladder ascariasis and described their ultrasonographic findings.

In keeping with other reports[3,4], the majority of patients (61 per cent) in this study were young adult women, three of whom were pregnant. Pregnant women may be more susceptible to biliary ascariasis owing to the relaxant effect of hormones on the smooth muscle of the bile ducts[5]. Two of these women had spontaneous passage of worms and the third needed cholecystectomy.

Biliary ascariasis in general has a good response to conservative treatment[2,3]. This may not hold true for gallbladder ascariasis. In this study only ten of 47 patients expelled the worms spontaneously, while 37 failed to respond to conservative treatment and required surgical intervention.

Gallbladder ascariasis is a significant entity in endemic areas, affecting mainly young adult women, which may present as acalculus cholecystitis or empyema of the gallbladder. It usually requires laparotomy and cholecystectomy although, in some cases, worms may migrate spontaneously to the common bile duct and be excreted. Ascariasis may cause a potentially fatal complication such as gallbladder empyema, septicaemia or pericholecystic abscess.

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Original article

Prospective study of chronic pain after groin hernia repair

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Background: The aim was to provide a detailed description of any residual pain 1 year after elective day-case open groin hernia repair under local anaesthesia.
Methods: This was a prospective consecutive case series study by questionnaire of 500 consecutive operations in 466 unselected adult patients 1 year after surgery. Pain was scored (none, mild, moderate or severe) at rest, while coughing and during mobilization, and compared with similar data collected 1 and 4 weeks after operation.
Results: Some 419 questionnaires were returned (response rate 93 per cent); 20 patients had died within the year and 30 data sets from patients who had a subsequent operation during the study were excluded. Eighty patients (19 per cent) reported some degree of pain, and 25 (6 per cent) had moderate or severe pain. Pain restricted daily function in 24 patients (6 per cent). The incidence of moderate or severe pain was higher after repair of recurrent than primary hernias (14 *versus* 3 per cent; $P < 0.001$). The risk of developing moderate or severe pain was increased in patients who had a high pain score 1 week after operation (9 *versus* 3 per cent; $P < 0.05$) and also in patients who had moderate or severe pain 4 weeks after operation (24 *versus* 3 per cent; $P < 0.001$).
Conclusion: Chronic pain is a significant problem after open groin hernia repair. It may be worse after surgery for a recurrent hernia and may be predicted by the intensity of early postoperative pain.

Paper accepted 3 September 1999

British Journal of Surgery 1999, **86**, 1528–1531

Introduction

The time course of acute pain after groin hernia repair is well documented[1,2]. Although late or chronic pain after inguinal hernia repair is a well known complication, data from large consecutive prospective studies are rare. The reported incidence of chronic pain after open hernia repair varies from 0 to 12 per cent[3–11]. The intensity of acute postoperative pain may be important for predicting the development of chronic pain after leg amputation, breast surgery and thoracotomy[12], but no data are available after hernia repair. This was a prospective study of the incidence of late pain 1 year after 500 consecutive open groin hernia repairs.

Patients and methods

Data were collected prospectively and consecutively from all adult patients admitted for day-case elective repair of a reducible inguinal or femoral hernia under local anaesthesia between 1 September 1994 and 31 August 1996. Five hundred hernias were repaired in 466 patients. During the study, 24 additional patients had an elective hernia repair under general anaesthesia owing to an irreducible hernia, lack of cooperation, refusal of local anaesthesia or laparoscopic repair. Data from these patients were not included.

Unmonitored local anaesthesia (bupivacaine) and sedation (midazolam) was provided by the surgeon. The different surgical techniques involved both mesh repair and sutured repair[13–15] (*Table 1*). Management of perioperative pain was standardized and consisted of tenoxicam before operation and for the first 4 days afterwards, two doses of oral methadone on the day of surgery and paracetamol as needed[16].

Cumulated pain scores (CPSs) from the first week after operation and pain scores obtained after 4 weeks have been reported previously[2]. The CPS is a calculated sum of daily pain scores for the first 7 days after operation. Pain scores for each day on a four-point verbal scale (none, mild, moderate or severe pain) were assigned the numerical values 0–3. Thus the CPS was a number in the range 0–21. The CPS was calculated for each condition (rest, cough and mobilization).

Table 1 Frequency of moderate or severe pain 1 year after each of the different hernia repairs in 419 respondents

Hernia type and surgical technique	No. of respondents	No. with moderate or severe pain
Primary direct; Lichtenstein mesh repair	127	6
Primary indirect; sac extirpation	21	0
Primary indirect; anulorrhaphy + sac extirpation	110	2
Primary indirect; modified Lichtenstein mesh repair	54	2
Primary femoral; mesh repair	8	1
Recurrent inguinal; Lichtenstein mesh repair	83	12
Recurrent femoral; mesh repair	7	1
Other types of surgery*	9	1
Total	419	25

*One recurrent femoral and eight recurrent inguinal

One year after surgery a questionnaire with a prestamped return envelope was mailed to each patient, requesting information about pain, use of analgesics, restriction of daily function and visits to a physician owing to pain in the groin within the past month. Patients were asked whether they had experienced pain related to the hernia within the past month, and the pain was scored during rest, cough and mobilization (rising to sitting position) on the four-point verbal scale.

Descriptive statistics were used for the demographics and pain course; the χ^2 test with Yates correction was used to evaluate differences in pain frequency and 5 per cent was chosen as the level of significance.

The study was approved by the local ethics committee and the Danish Data Protection Agency. Patients gave written informed consent before participation.

Results

Five hundred operations were performed in 466 patients. Thirty-two patients had two or more operations during the study, for independent bilateral hernias (19 patients) or recurrence of the hernia (13); one of the latter had three operations for two recurrences. These patients were excluded to avoid the influence of pain from the second operation unless 1 year had passed between operations. Median patient age was 60 (interquartile range 44–74) years at the time of surgery. According to the American Society of Anesthesiologists classification, 287 patients were grade I, 175 grade II and 38 grade III. There were 448 men and 52 women.

Thirty data sets from patients undergoing more than one hernia operation during the study were excluded, as less than 1 year had passed between operations. Twenty patients had died within the observation period. Of the remaining 450 questionnaires, 419 were returned 1 year after hernia repair, resulting in a response rate of 93 per cent. All frequencies were calculated in relation to the number of respondents.

Pain of some degree during rest, coughing or mobilization was reported by 80 patients (19 (95 per cent confidence interval 15–23) per cent), and 25 (6 (4–8) per cent) reported moderate or severe pain. Mild pain was reported by 55 patients (13 (10–16) per cent). Some 339 patients reported no pain at all. Nine patients (2 (1–4) per cent), all with moderate or severe pain, used analgesics. Of patients reporting hernia-related pain 1 year after operation, 24 (6 (4–8) per cent) considered that it restricted their level of function, and ten (2 (1–4) per cent) had visited a physician within the past month because of hernia-related pain.

The frequency of moderate or severe pain for each of the different hernia repairs is described in *Table 1*. Patients treated for a recurrent hernia had a significantly higher incidence of moderate or severe pain than patients after primary repair (14 *versus* 3 per cent; $\chi^2 = 13\cdot6$, 1 d.f., $P < 0\cdot001$). Similarly, moderate or severe pain was more common after Lichtenstein mesh repair for a recurrent hernia than after primary Lichtenstein repair (14 *versus* 5 per cent; $\chi^2 = 4\cdot89$, 1 d.f., $P < 0\cdot05$). There was no significant difference in the incidence of pain after all primary mesh repairs and non-mesh repairs (5 *versus* 2 per cent; $\chi^2 = 1\cdot56$, 1 d.f., $P > 0\cdot2$).There were no significant differences between the no or mild pain and the moderate or severe pain groups with respect to age and sex.

Pain scores after 1 year were compared with those obtained 1 and 4 weeks after operation. The frequency of moderate or severe pain after 1 year was significantly higher in patients with a CPS of 11 or more than in patients with a lower CPS (9 *versus* 3 per cent; $\chi^2 = 5\cdot64$, 1 d.f., $P < 0\cdot05$) (*Table 2*). Likewise, the frequency of moderate or severe pain after 1 year was higher in patients with moderate or severe pain after 4 weeks (24 *versus* 3 per cent; $\chi^2 = 28\cdot5$, 1 d.f., $P < 0\cdot001$).

Table 2 Number of patients with moderate or severe pain 1 year after operation compared with cumulated pain scores from the first week after operation and pain data after 4 weeks

	1 year after operation	
	Respondents ($n = 419$)	Moderate or severe pain ($n = 25$)
Week 1		
CPS ≤ 10	222	7 (3)*
CPS ≥ 11	197	18 (9)
End of week 4		
No or light pain	359	12 (3)†
Moderate or severe pain	46	11 (24)
No response	14	2

Values in parentheses are percentages. CPS, cumulated pain score *$P < 0.05$ *versus* CPS ≥ 11; †$P < 0.001$ *versus* patients with moderate or severe pain (χ^2 test)

Haematoma (eight patients) or infection (eight) requiring surgical drainage occurred after 16 of the 500 operations. Two of these patients, both with infection after a Lichtenstein mesh repair (one recurrent and one primary direct hernia), reported moderate or severe late pain 1 year after operation.

Discussion

The true incidence of chronic pain after hernia repair remains to be documented; data from large consecutive series with late follow-up are rare. In a study including 460 patients with a 92 per cent follow-up rate, Töns and Schumpelick[9] found that 3 per cent had persistent pain 12 months after open hernia repair, Payne *et al.*[6] found a rate of 4 per cent in 50 patients 6 months after open repair, and Davies and Horrocks[17] found in 100 patients that nine of 82 responders had mild pain 1 year after open hernia repair. Cunningham *et al.*[18] demonstrated that 12 per cent of respondents (315 of 883 patients; 36 per cent response rate) had moderate or severe pain 1 year after open hernia surgery. None of these four studies provided a detailed description of any limitation in daily function, although both walking difficulties and sexual dysfunction were mentioned. Liem *et al.*[19] have reported significantly more patients with chronic pain 6 months after open than after laparoscopic repair (14 *versus* 2 per cent). Other studies have not demonstrated any significant differences[4–6,20,21]. No study has compared different anaesthetic or analgesic techniques, and the need for treatment of persistent pain has not been quantified or described in detail in any consecutive series.

The primary findings in the present large-scale consecutive study with a follow-up rate of 93 per cent were that 19 per cent of the patients still had pain during rest or function 1 year after operation, that in 6 per cent the pain interfered with daily function, and that 6 per cent reported moderate or severe pain. Patients treated for a recurrent hernia had a fourfold higher rate of moderate or severe pain than those treated for a primary hernia. The rate of moderate or severe pain was almost three times higher after recurrent hernia repair even when a Lichtenstein mesh repair was used. A sevenfold increase in the frequency of moderate or severe pain after 1 year was reported in patients who had a high pain score 4 weeks after operation compared with those with a low pain score.

The rate of moderate or severe pain (6 per cent) was approximately half of that found after 4 weeks[2], but was still of clinical significance and comparable to that seen in previous small-scale studies[4,6]. The impact of the pain is illustrated by the number of patients who used analgesics, felt restricted in their daily function or visited their physician within the past month with hernia-related pain.

Mesh repair has become very popular. Its tension-free properties should lead to less acute postoperative pain. However, in randomized studies it has not proven superior to other open repair techniques with respect to acute pain or use of analgesics[2,22]. In the present study the incidence of moderate or severe late pain was quite high after mesh repair. Chronic pain after mesh repair has been described recently in 20 patients[23], in whom surgical intervention had only a modest success rate (60 per cent). The incidence of chronic pain after mesh repair remains debatable, although it is reported to be very low from dedicated hernia centres[24–26].

The increased incidence of chronic pain in patients with a high pain score after 1 and 4 weeks found in the present study may have a number of explanations. Nerve injury at the time of operation may be an important mechanism; alternatively a high initial pain intensity may induce neuroplastic changes in the central nervous system leading to chronic pain. Unfortunately, the questionnaires in the present study did not differentiate between somatic and neuropathic pain. Cunningham *et al.*[18] also reported late pain to be related to the intensity of immediate postoperative discomfort, although data were not presented to support the statement.

Chronic pain remains a significant clinical problem after open hernia repair. High initial pain scores and surgery for recurrent hernia both increase the risk of developing chronic pain after open hernia surgery.

Acknowledgements

This study was supported by a research grant from ASTRA Pain Control, Södertälje, Sweden, and quality assurance funds from the Copenhagen Hospital Corporation.

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Original article

Clinicopathological study of intrapelvic cancer spread to the iliac area in lower rectal adenocarcinoma by serial sectioning

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Background: The role of iliac lymphadenectomy in surgery for rectal cancer remains unknown. Detailed clinicopathological data on lateral cancer extension may be needed to determine the true role of this procedure.

Methods: Seventy consecutive patients with low rectal cancer who underwent systematic iliac lymphadenectomy between 1991 and 1995 were reviewed. The iliac area was divided into five regions: (1) middle rectal root, (2) internal iliac, (3) obturator, (4) common iliac and (5) external iliac. Iliac lymph nodes that were cancer-free based on conventional pathological examination were serially sectioned at 100-μm intervals and re-examined for occult microscopic involvement.

Results: Occult microscopic foci were detected in five (7 per cent) of the 70 patients, and the overall incidence of lateral cancer spread was 24 per cent (17 of 70). Among patients without other sites of distant metastasis or circumferential involvement of the margin, the 5-year survival rate of those with lateral spread was 35 per cent. Although the prognosis of patients with cancer involving multiple iliac regions was poor, three of six patients with metastasis to only a single region were alive without disease at 3 years.

Conclusion: Surgeons should be aware of the possibility of localized lateral spread, including microscopic metastasis, when determining the optimum procedure for iliac lymphadenectomy in patients with rectal cancer.

Paper accepted 8 July 1999

British Journal of Surgery 1999, 86, 1532–1537

Introduction

The optimum surgical treatment for preventing local recurrence of rectal cancer is subject to continuing debate. Recently, systematic iliac lymphadenectomy, which is frequently performed in Japan, has attracted the attention of Western surgeons[1–5]. The clinical importance of the lateral spread of primary lower rectal cancer was first demonstrated in the early 1950s[6–8]. Since then, the potential benefits of systematic abdominopelvic lymphadenectomy with lateral dissection have been reported mainly by Japanese surgeons[9–12].

In Western countries, on the other hand, the advantages of iliac lymphadenectomy are regarded as questionable because: (1) lateral lymph node metastasis does not occur so frequently[7,13,14]; and (2) lateral spread of this cancer is a form of systemic spread and is not regional disease[2,15].

The lymphatic drainage system of the rectum has long been studied[13,14,16–19] and the notion of cancer spread in the mesorectum has been developed[20–23] as the basis for total mesorectal excision[15,24–26]. However, few intensive studies of lateral cancer spread outside the mesorectum, with a special focus on microscopic metastasis, have been reported[27].

The present study aimed to address the pathological extent of lateral cancer spread and the outcome of patients with this type of spread.

Patients and methods

Patients

Between January 1991 and December 1995, 166 patients underwent operation for rectal cancer below the peritoneal reflection. During this period, among the patients who had advanced cancer without irresectable distant metastatic disease, systematic iliac lymphadenectomy was carried out when transmural penetration of the primary tumour or pararectal lymph node involvement was strongly suspected, provided this was allowed by other clinical factors (i.e. operative risk and patient consent). A total of 70 patients underwent operation combined with bilateral systematic iliac lymphadenectomy; they were reviewed retrospectively. These patients comprised 47 men and 23 women with a mean age of 58·8 (range 25–77) years. Sphincter-saving surgery was performed in 24 patients, abdominoperineal resection in 41 and total pelvic exenteration in five. Among the six patients with distant metastasis, three had liver metastasis in one lobe, one had localized dissemination to the adjacent peritoneum and two had non-regional (mesosigmoid) lymph node metastases, so the metastases were all resectable. Two patients, one with non-regional nodal metastases, had circumferential involvement of the margin pathologically, although the primary tumour was curatively resected macroscopically. No patient in this series received preoperative neoadjuvant therapy. The clinicopathological features of all resected cancers are shown in *Table 1* based on the Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum)[28].

Table 1 Clinicopathological background of patients undergoing systematic iliac lymphadenectomy

Category	No. of patients
Location of tumour distal edge	
Rectum	44 (63)
Anal canal	26 (37)
Median (range) maximum diameter (cm)	5·7 (2.0–12.0)
Pathological type	
Well differentiated	10 (14)
Moderately differentiated	54 (77)
Poorly differentiated	3 (4)
Mucinous carcinoma	2 (3)
Signet-ring cell carcinoma	1 (1)
Lymphatic invasion	
None	1 (1)
Mild	30 (43)
Moderate	32 (46)
Significant	7 (10)
Venous invasion	
None	4 (6)
Mild	28 (40)
Moderate	29 (41)
Significant	9 (13)
Tumour depth	
Muscular layer	6 (9)
Beyond rectal wall	54 (77)
Invasion to other organs	10 (14)
Mesenteric node involvement	
None	21 (30)
Pararectum	38 (54)
Inferior mesenteric trunk nodes	5 (7)
Inferior mesenteric root nodes	4 (6)
Non-regional nodes*	2 (3)
Distant metastasis	
No	64 (91)
Yes	6 (9)

Values in parentheses are percentages. *Mesosigmoid nodes

Division of the iliac area

The iliac area was classified into five divisions, including (1) the middle rectal root region (along the middle rectal artery lateral to the pelvic plexus), (2) the internal iliac region (along the internal iliac artery), (3) the obturator region (along the obturator nerve, artery and vein), (4) the common iliac region (along the common iliac artery) and (5) the external iliac region (along the external iliac artery). These regions were defined according to the Japanese Classification of Colorectal Carcinoma[28] (*Fig. 1*).

Serial sectioning and examination

The lymph nodes and other tumour deposits in the iliac region were fixed in formalin, sectioned along the midline and stained with haematoxylin and eosin; the presence of cancer in these specimens was determined by histopathological examination. Specimens judged to contain no cancer by conventional examination were then serially sectioned at 100-µm intervals, stained with haematoxylin and eosin, and examined for the presence of micrometastases. The total number of iliac lymph nodes and nodules examined in this serial sectioning study was 2051, and the mean number per patient was 29·3.

All patients were followed for longer than 3 years or until death, and the mean length of follow-up for survivors was 61

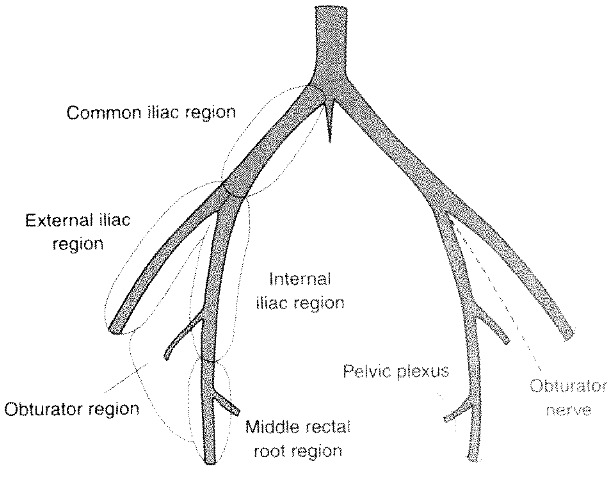


Fig. 1 Diagram showing division of the iliac area

(range 36–89) months. In the prognostic study, 64 patients who demonstrated no distant metastases were investigated. Survival curves were created with the Kaplan–Meier method, and the log rank test was used for comparisons. Various clinicopathological variables were analysed to detect any associations with cancer spread to the iliac area, using the χ^2 test and Fisher's exact method when necessary.

Results

Incidence of cancer spread to the iliac area

Fifteen patients were diagnosed as having iliac lymph node metastases by conventional pathological examination. Occult microscopic cancer foci were detected in other iliac divisions by serial sectioning in three of these patients. Moreover, serial sectioning detected microscopic lateral spread in two of the patients who were diagnosed as having no iliac nodal metastases by conventional examination. As a result, a total of 17 (24 per cent) of 70 patients was found to have extension of cancer to the iliac area. One patient had circumferential margin involvement pathologically and also had non-regional lymph node metastases. Occult metastatic foci were observed not only in the lymph nodes, but also in the extranodal tissues (two cases).

The distribution of lateral cancer spread including occult microscopic foci is shown in *Table 2*. The middle rectal root region showed the highest incidence of involvement, and three-quarters of the patients with lateral spread had involvement of this region. Eight patients had involvement of only one iliac region, whereas the others showed involvement of multiple iliac regions.

Pathological features of primary tumours with spread to the iliac area

No differences in the rate of involvement of the iliac region were observed after stratification for tumour diameter and location. Patients with more deeply penetrating tumours showed a higher incidence of spread to the iliac region, but the difference was not significant (*Table 3*). The mean(s.d.) number of positive mesorectal nodes in patients with cancer spread to the iliac region (4·6(5·9)) was much higher than for patients without it (1·9(2·6)) ($P = 0·017$). Other parameters with a significant impact on lateral extension were the pathological type, lymphatic invasion and venous invasion. Cancer spread to the iliac area was frequently observed in cases of poorly differentiated adenocarcinoma and mucinous carcinoma (four of five cases), as well as when the metastatic lymph nodes were beyond the pararectal area (three of seven cases) (*Table 3*).

Table 2 Divisions of the iliac area and the actual distribution of cancer spread

Division of iliac area	Positive cancer spread*
Middle rectal root region	13 (19)
Internal iliac region	6 (9)
Obturator region	6 (9)
Common iliac region	3 (4)
External iliac region	5 (7)

Values in parentheses are percentages. *Detected by conventional and/or serial section examination

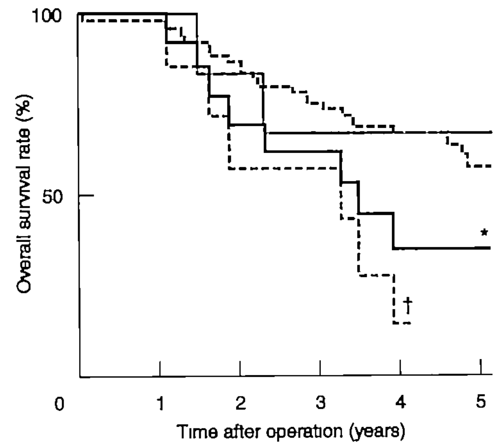
Prognosis of patients with involvement of the iliac area

Four (two with single region and two with multiple region involvement) of the six patients with distant metastases were found to have iliac nodal involvement. All these patients had recurrence in multiple distant organs and died within 2 years. On the other hand, no statistically significant difference ($P = 0·07$) was observed among patients with neither distant metastases nor circumferential involvement, although the survival rate of those with cancer metastasis to

Table 3 Relationship between cancer spread into the iliac area and other clinicopathological characteristics in patients without distant metastases or circumferential margin involvement

	Cancer in the iliac region*		P
Characteristic	Negative ($n = 50$)	Positive ($n = 13$)	
Depth of penetration			
Muscular layer	5	1	n.s.†
Beyond rectal wall	38	9	
Invasion to other organs	7	3	
Mesenteric node involvement			
None	18	3	n.s.†
Pararectum	28	7	
Inferior mesenteric trunk or root	4	3	
Pathological type			
Well differentiated	9	1	0.0053‡
Moderately differentiated	40	8	
Poorly differentiated or mucinous	1	4	
Lymphatic invasion			
None or mild	29	1	0.0012†
Moderate or significant	21	12	
Venous invasion			
None or mild	27	2	0.0128†
Moderate or significant	23	11	

*Including occult microscopic involvement. †χ^2 test; ‡well and moderately differentiated *versus* poorly differentiated and mucinous (Fisher's exact method)



No at risk	0	1	2	3	4	5
Positive	13	13	9	8	4	1
Single region (+)	6	6	5	4	3	1
Multiple region (+)	7	7	4	4	1	0
Negative	50	49	42	38	26	19

Fig. 2 Comparison of survival of patients without distant metastases or circumferential margin involvement undergoing systematic iliac lymphadenectomy based on the extent of iliac nodal involvement:
——— patients with cancer involving the iliac area ($n = 13$);
- - - - - - patients without cancer spread involving the iliac area ($n = 50$);
——— patients with cancer spread to a single iliac region ($n = 6$);
- - - - - - patients with cancer spread to more than one iliac region ($n = 7$).
$^*P = 0{\cdot}07$, $^\dagger P = 0{\cdot}007$ *versus* no iliac involvement (log rank test)

the iliac region was worse than that of patients without it (*Fig. 2*). The 5-year survival rate of the former group of patients was 35 per cent, and six of the 13 patients had local pelvic recurrence. In contrast, 16 per cent (eight of 50) of the patients without iliac nodal involvement had pelvic recurrence, which was almost always associated with simultaneous recurrence in another distant organ. Pelvic recurrence occurred within the lateral region in half (four of eight patients). Among patients with lateral cancer spread, the prognosis of those with metastases to multiple iliac regions was extremely poor (*Fig. 2*) and five of the seven patients showed local pelvic recurrence. However, four of the six patients with iliac disease localized to a single region were alive at 3 years, and pelvic recurrence occurred in only one patient, despite the fact that no intensive adjuvant therapy was received until recurrence occurred.

Discussion

One of the most common sites of recurrence after curative resection of rectal cancer is the pelvis[29], and local control is a major goal of surgical treatment. Appropriate dissection to eliminate residual cancer foci, such as involved lymph nodes, is necessary to achieve local control. However, the target region for local recurrence remains controversial. Some Japanese surgeons place great emphasis not only on total mesorectal excision but also on intrapelvic lateral lymph node dissection, whereas the latter procedure is performed only rarely in Western countries. There are several possible reasons for this difference of opinion regarding the clinical significance of iliac lymphadenectomy.

The first reason might be variation in the incidence of intrapelvic lateral cancer spread. Early Western anatomical studies reported that lateral lymph node metastasis occurred in 2–12 per cent of all patients[7,13,14]. However, spread beyond the mesorectum is believed to occur more frequently in Japan, and subsequent Japanese studies have also demonstrated a higher rate of lateral lymph node metastasis (11–23 per cent) in patients with advanced lower rectal cancer[11,12,30–32]. In the present study, 24 per cent of patients who underwent systematic bilateral lateral node dissection had cancer in the iliac region, including microscopic foci that were detected only by serial sectioning. It is noteworthy that four of the seven patients with involvement of either the inferior mesenteric trunk nodes or the inferior mesenteric root nodes had residual lateral cancer foci despite the fact that total mesorectal excision was performed. Furthermore, pelvic recurrence occurred within the iliac region in half of the patients whose lateral node involvement was not apparent, raising the possibility of undetected residual iliac disease owing to incomplete resection. The high incidence of cancer spread beyond the mesorectum should therefore not be overlooked when discussing the origin of local recurrence.

The second reason why iliac lymphadenectomy is not popular in Western countries is that lateral cancer spread is regarded as systemic spread, and not as regional disease[2,15]. It has been pointed out that other metastatic foci are often present in patients with lateral spread, and that the survival rate may not be improved even if local control is achieved[15]. This concept has been further supported by some unfavourable reports on the results of radical lymphadenectomy[32–34]. However, Stearns and Deddish[33] reported evidence of the effectiveness of extended lymphadenectomy in 1959; two of 11 patients who underwent abdominopelvic lymphadenectomy were found to have metastases in the abdominopelvic extramesenteric lymph nodes (which would not have been removed by the usual Western procedure) and both patients lived for 5 years or more. Furthermore, systematic lymphadenectomy with lateral dissection has been reported by Japanese researchers to decrease local recurrence and enhance survival[9–12]. The prognosis of patients with iliac node involvement was worse than that of those without such involvement in the present series. However, 35 per cent of patients with iliac metastasis clearly benefited from iliac lymphadenectomy. This procedure was advantageous for patients in whom lateral cancer spread was localized to a single region on serial sectioning, in terms of both local control and long-term survival. Although the present patient population was small, which might be the reason why the 5-year survival rate of patients with no lateral spread seemed to be worse than that of patients with involvement of one region, it appears that not all iliac nodal involvement necessarily represents systemic disease.

The main route of cancer spread to the lateral region has been reported to be along the middle rectal and pudendal arteries[30,35], where the inferior hypogastric plexus lies in close proximity, and involvement of this region was the most common finding in the present study. The third reason for a negative opinion regarding the use of lateral lymphadenectomy in the West is the negative influence of this procedure on the postoperative quality of life. Radical lateral lymphadenectomy invariably damages the inferior hypogastric plexus, thus resulting in urinary dysfunction and impotence[1,36].

It is therefore thought to be excessive to perform pelvic lymphadenectomy routinely while also sacrificing the autonomic nerves as a standard operation for rectal cancer. The present study cannot answer the core question as to whether the procedure should be performed or not. A larger database is needed to determine the optimum way of identifying a subset of candidates for resection in whom lateral disease can be regarded as local. Prospective randomized studies are essential to corroborate the value of iliac lymphadenectomy.

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Original article

Nitric oxide synthetase and *Helicobacter pylori* in patients undergoing appendicectomy

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Background: This study was designed to determine whether *Helicobacter pylori* forms part of the normal microenvironment of the appendix, whether it plays a role in the pathogenesis of acute appendicitis, and whether it is associated with increased expression of inducible nitric oxide synthetase (iNOS) in appendicular macrophages.

Methods: Serology for *H. pylori* was performed on 51 consecutive patients undergoing emergency appendicectomy. Appendix samples were tested for urease activity, cultured and stained for *H. pylori*, graded according to the degree of inflammatory infiltrate, and probed immunohistochemically for iNOS expression.

Results: The mean age of the patients was 21 (range 7–51) years. Seventeen patients (33 per cent) were seropositive for *H. pylori* but no evidence of *H. pylori* was found in any appendix specimen. However, an enhanced inflammatory cell infiltration was observed in seropositive patients ($P < 0{\cdot}04$) and the expression of macrophage iNOS in the mucosa of normal and inflamed appendix specimens was increased ($P < 0{\cdot}01$).

Conclusion: *H. pylori* does not colonize the appendix and is unlikely to be a pathogenic stimulus for appendicitis. Priming effects on mucosal immunology downstream from the foregut may occur after infection with *H. pylori*.

Paper accepted 4 July 1999

British Journal of Surgery 1999, 86, 1538–1542

Introduction

Helicobacter pylori is associated with a variety of upper gastrointestinal conditions[1]. It is an aetiological factor in duodenal ulcers (up to 95 per cent of cases), type B gastritis and gastric mucosa-associated lymphoid tissue (MALT) B-cell lymphoma[2–6]. The World Health Organization has recently classified *H. pylori* as a grade 1 (definite) carcinogen in the pathogenesis of gastric carcinoma[7]. *H. pylori* infestation of the upper gastrointestinal tract can induce the appearance of lymphoid aggregates (MALT) that are not normally present in the stomach[8]. Successful culture of *H. pylori* from the human mouth, dental plaque and faeces supports the view that the organism survives outside an acidic environment[4]. Similarly, the stimulatory effect of *H. pylori* on MALT is not confined to the upper gastrointestinal tract. The organism has been reported in association with low-grade B-cell lymphoma of the rectum, with complete histological remission following eradication of *H. pylori*[5].

Certain strains of *H. pylori*, possessing the cytotoxin-associated gene, exert direct cytotoxic effects on the mucosal epithelium and potentiate tissue damage by stimulating an inflammatory response in the mucosa and submucosa[9–11]. The organism produces highly stable products that penetrate the lamina propria and increase the expression of inducible nitric oxide synthetase (iNOS) in mucosal macrophages[12]. The expression of iNOS is increased when both live and lysed samples of *H. pylori* are introduced to the stomach[13]. Subsequent production of nitric oxide enhances chemotaxis and proinflammatory cytokine release[14]. Indeed, the stable products of *H. pylori* alone are sufficient to stimulate a cytokine response in host tissues[10]. A similarly high expression of mucosal iNOS in inflammatory bowel disease, combined with the finding that iNOS inhibition ameliorates experimental colitis, underlines the pivotal role of this enzyme in immunological events[15–17].

Acute appendicitis is the most common surgical emergency, with 16 per cent of the population undergoing appendicectomy[18]. The exact aetiology is ill defined but an infective origin has been proposed owing to the fluctuating incidence of appendicitis during this century[19]. Appendicitis begins with mucosal inflammation which subsequently spreads to the serosal surface resulting in peritonitis. Abscess formation or perforation occurs in 25 per cent of patients. It was postulated that *H. pylori* infection could cause MALT hypertrophy in the appendix to the point that, under certain conditions, luminal obstruction and acute appendicitis might occur. It is possible that an inflammatory response could be primed, because of the presence of *H. pylori* or its products, by enhanced mucosal macrophage iNOS expression (as occurs in the foregut)[20].

This study was designed to ascertain whether *H. pylori* forms part of the microenvironment of the appendix, whether there is an association between *H. pylori* serology and acute appendicitis, and whether *H. pylori*-positive patients have an increased expression of iNOS in appendicular macrophages.

Patients and methods

All patients undergoing emergency appendicectomy over 4 months were included in the study irrespective of age, co-morbid disease or the pathological status of the appendix. Antibiotic prophylaxis (metronidazole) was administered on induction of anaesthesia. Appendix specimens were sent for routine histopathological analysis and, using a predetermined grading system, were given a score (0–3) by a single, blinded, pathologist depending on the extent of inflammation (*Table 1*). At the time of pathological analysis all specimens were also examined for *Helicobacter*-like organisms using a modified Giemsa stain[21].

Two small (1 cm) 'doughnut' biopsies were taken from the appendix base before placement of the specimen in formalin. One was transported to the microbiological laboratory in a physiological saline solution for *H. pylori* culture and the other was placed in a CLOtest (Tri-Med, Draper, Utah, USA) to identify urease activity. Biopsies were minced and inoculated on blood agar with selective supplement added (Dent and McNulty; Oxoid, Basingstoke, UK) for culture. Plates were incubated for 10 days in a humid microaerobic atmosphere at 37°C. The study policy dictated that any specimen deemed to be positive for *H. pylori* would undergo polymerase chain reaction (PCR) to identify the specific *H. pylori* strain[21]. Positivity was considered when any specimen fulfilled two of the following criteria: urease activity, *H. pylori* growth or identification with Giemsa staining.

Table 1 Grading system for acute appendicitis based on pathological findings

Description	Grade	Pathological status
Normal	0	No evidence of inflammation
Mild	1	Inflammatory infiltrate confined to mucosa with no serosal or peritoneal reaction
Moderate	2	Transmural inflammation with serosal or peritoneal reaction, but no perforation or abscess formation
Severe	3	Evidence of perforation, gangrene or abscess formation

Mucosal macrophage iNOS expression in appendix samples was assessed by immunocytochemistry. In brief, specimens were dewaxed with xylene and alcohol solutions, and endogenous peroxidase activity was blocked using 3 per cent hydrogen peroxide in distilled water. Specimens were then rinsed, placed in Tris buffered saline (TBS) and a serum-free protein block was applied to sections. Primary antibody to iNOS was applied (murine cultured antihuman iNOS immunoglobulin (Ig) G; Transduction Laboratories, supplied by Affiniti Research Products Limited, Exeter, UK) and the samples were then rinsed in TBS. Secondary antibody (Duet-Dako K0492; Dako, Cambridge, UK) was applied for 35 min and the slides were again rinsed in TBS. The tertiary layer (Duet K04920; Dako) was applied for 35 min and then rinsed with TBS. 3,3-Diaminobenzidine tetrahydrochloride dihydrate (DAB; Kem-en-Tec) was applied to slides for 10 min, followed by Haemalum for 2 min (haematoxylin stain). Slides were then dehydrated with alcohol and xylene before the application of coverslips. Gastric mucosal biopsies expressing mucosal macrophage iNOS (from *H. pylori*-positive patients) and β-actin, serving as positive and negative controls respectively, were used to confirm the specificity of the assay (greater than 98 per cent). All samples were assessed for mucosal macrophage iNOS activity at × 40 magnification, with a positive result defined as one or more positively stained macrophage cells per field. In addition, the ratio of positive to negative staining macrophages per field was determined to give an estimate of activity.

On the first postoperative day 7 ml blood was drawn for *H. pylori* serology using a premier *H. pylori* IgG enzyme-linked immunosorbent assay (ELISA) (Meridian Diagnostics, supplied by Launch Diagnostics, Kent, UK). This method offers 95–100 per cent sensitivity and specificity for *H. pylori*[22]. The seropositivity of 50 age- and sex-matched asymptomatic volunteers without previous appendicectomy was also assessed. Any history of previous *H. pylori* status or eradication was noted. The patient's general practitioner was contacted and informed of any positive serological results.

Analysis of variance was employed for statistical analysis; $P < 0.05$ was considered significant.

Results

Fifty-one consecutive patients presenting with symptoms and signs of acute appendicitis were enrolled. Emergency open appendicectomy was performed within 48 h of the onset of symptoms in all patients. The mean age was 21 (range 7–51) years and the male : female ratio was approximately 2 : 3. Forty patients (78 per cent) had a pathologically abnormal appendix, with faecoliths identified in seven patients (14 per cent). No patient had malignancy detected on macroscopic or microscopic examination of the appendix.

Multiple organisms were grown from all appendix specimens but only three appendiceal 'doughnut' biopsies were positive for urease activity on the CLOtest. There was no growth of *H. pylori* from the samples, even in selective culture. Rather, *Proteus* species were identified as the organisms with urease activity. Similarly, there was no evidence of *H. pylori* in any sample on histological assessment following Giemsa staining. Therefore, all appendix specimens were considered to be negative for *H. pylori*, and strain typing by PCR was not performed.

The appendix was histologically normal in 14 patients (27 per cent). There was a slight preponderance of negative appendicectomies in the *H. pylori*-negative group (11 of 34 *versus* three of 17) but this was not statistically significant ($P > 0{\cdot}05$). Similarly, the rate of *H. pylori* seropositivity in patients with a normal appendix was similar to that in patients with an inflamed appendix (three of 14 *versus* 14 of 37; $P > 0{\cdot}05$). The rate of *H. pylori* seropositivity in the matched control group of asymptomatic volunteers without previous appendicectomy was 14 (28 per cent) of 50. This was not significantly different from the seropositive rate in patients with an inflamed appendix (14 (38 per cent) of 37; $P > 0{\cdot}05$) or in all patients who had an appendicectomy (17 (33 per cent) of 51; $P > 0{\cdot}05$).

The results of the pathological grading according to the degree of inflammatory infiltrate in the layers of the appendix are shown in *Table 2*. The grading was evenly distributed among the four categories. However, 13 of the 17 appendix specimens from seropositive patients had high histological grade appendicitis (2 or 3), compared with 13 of the 34 *H. pylori*-negative patients ($P < 0{\cdot}04$).

All appendix specimens were probed for mucosal macrophage iNOS. Thirty (59 per cent) of the total 51 specimens stained positively for mucosal macrophage iNOS. Overall, patients with positive *H. pylori* serology had a higher expression of mucosal macrophage iNOS than *H. pylori*-negative patients (14 of 17 *versus* 16 of 34; $P < 0{\cdot}01$). Moreover, mucosal macrophage iNOS expression was greater in histologically normal appendix specimens from seropositive patients than in those from *H. pylori*-negative patients (17 of 34 *versus* nine of 34; $P < 0{\cdot}01$). Finally, the relative presence of mucosal macrophage iNOS, expressed as a percentage of mucosal macrophages per field, was significantly greater in *H. pylori*-seropositive than in *H. pylori*-negative patients (11 of 17 *versus* 13 of 34; $P < 0{\cdot}03$).

Table 2 Grade of acute appendicitis and *Helicobacter pylori* serology

	Grade				
	0	1	2	3	Total
H. pylori					
Positive	3	1	10	3	17
Negative	11	10	10	3	34
Total	14	11	20	6	51

Discussion

The aetiology of appendicitis is poorly understood. It has been proposed, on the basis of epidemiological data including case clustering and seasonal fluctuation, that infection may be the primary event[18,19]. In this study, the possibility that a relationship exists between *H. pylori* status and appendicitis was explored.

The results suggest that *H. pylori* is not a component of the microflora of the normal or inflamed appendix. In support of this, a recent study of ten patients with acute appendicitis failed to demonstrate *H. pylori* from the appendix using PCR techniques[23]. However, only one of the ten patients in that study was *H. pylori*-positive on serological testing. In the present study, where one-third of the cohort was positive for *H. pylori* on the basis of serology, the organism was not cultured from appendix samples despite using specific techniques, nor was it found on histological analysis. It seems that *H. pylori* does not flourish in the environment of the appendix–ileocaecal region. *H. pylori* transforms into a fastidious coccal form when outside the acidic environment of the stomach[24]. It has been demonstrated in human faeces and can be grown from dental plaque and faecal samples even at pH 4 and higher[4,25]. This suggests that it is not only pH that prevents colonization of the appendix with *H. pylori*, but also local factors such as competitive growth inhibition by commensal organisms or a hostile immunological environment.

H. pylori stimulates an IgG response in the host and this has formed the basis for a range of ELISAs for detecting the presence of the organism. This method is the most popular for screening for *H. pylori* because of its low cost, availability and reproducibility[26]. The main drawbacks of serological testing are interassay variation and the poor sensitivity and specificity of some ELISA kits. Therefore, a single assay with a sensitivity and specificity of 95–100 per cent was employed in this study[22]. In keeping with expected background rates for a large rural area, 33 per cent of the cohort was positive for *H. pylori*[22]. The rate of histologically normal appendicectomies in this study (27 per cent) is comparable with that obtained by others[18]. The lack of difference in seropositivity rates does not support a relationship between *H. pylori* and appendicitis. In particular, the seropositivity rate of the study group was not significantly different from that found in a control group of asymptomatic volunteers without previous appendicectomy. Although it is difficult to draw firm conclusions based on a small sample, it seems unlikely that *H. pylori* is a direct pathogen in appendicitis.

Using a predetermined histological grading system, *H. pylori*-positive patients were found to have a significantly greater inflammatory infiltrate in the appendix. Moreover, samples taken from *H. pylori*-positive patients exhibited a higher expression of iNOS in mucosal macrophages than those from *H. pylori*-negative patients. This disparity of iNOS expression was particularly apparent in patients with a normal appendix. It has been established that *H. pylori* (or its surface proteins) activates macrophages by an endotoxin-independent mechanism, stimulates iNOS expression and activity, and induces an inflammatory infiltrate in the foregut[10,12–14,20]. It is possible that *H. pylori* (or its cellular products) 'prime' the appendix by inducing mucosal macrophage iNOS expression and more marked cytokine responses. Thus, although *H. pylori* does not colonize or infect the appendix, downstream effects of gastroduodenal infestation (including shed surface molecules from dying organisms) might induce a primed immunological state causing an enhanced inflammatory infiltrate to a second insult.

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Original article

Preliminary results of a multicentre trial of the electrically stimulated gracilis neoanal sphincter

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Background: The electrically stimulated gracilis neoanal sphincter was initially developed to treat refractory incontinence. Good early results were reported from the two centres that pioneered the technique. The aim of this study was to assess the operation in a prospective multicentre setting.

Methods: The procedure was performed on 64 patients from seven centres worldwide and was performed in stages. All patients were evaluated clinically and manometrically before and after operation.

Results: There was a high incidence of infective and hardware-related complications. At a median of 10 months following closure of the defunctioning stoma 56 per cent had experienced a good functional result. The major functional problems comprised evacuatory difficulties experienced by 25 per cent.

Conclusion: The technique is effective in treating otherwise refractory incontinence. It is, however, a complex procedure and the morbidity rate may be high, particularly during the learning curve, factors that necessitate careful patient selection.

Presented to the Association of Surgeons of Great Britain and Ireland in Bournemouth, UK, April 1997 and the European Council of Coloproctology in Edinburgh, UK, June 1997; and published in abstract form as *Br J Surg* 1997, 88(Suppl): 39 and *Int J Colorectal Dis* 1997; 12: 144

Paper accepted 15 July 1999

British Journal of Surgery 1999, **86**, 1543–1548

Introduction

Faecal incontinence is a common and debilitating symptom. It arises as a result of the congenital absence of, surgical removal of or pathological damage to the anorectum, anal sphincters, pelvic floor or their neurological pathways. Established surgical techniques, which include direct sphincter repair and postanal repair, provide relief for some patients[1,2]. Both these techniques, however, have an appreciable failure rate[3–5]. Furthermore a significant proportion of patients with congenital anorectal anomalies corrected in early life will be permanently incontinent[6]. A significant number of patients resort to a permanent stoma as the only way to control their symptoms. The physical and psychological sequelae of a permanent stoma are well documented[7,8]. The electrically stimulated gracilis neoanal sphincter (ESGN) was developed in the late 1980s for patients with intractable incontinence, refractory to existing treatment options, as an alternative to a permanent stoma.

Skeletal muscle neosphincters have been used to augment or reconstruct anal sphincters since the 1930s. The gracilis muscle was first used by Pickrell *et al.*[9] in the 1950s and has become the muscle of choice. It is morphologically suited to transposing around the anal canal and there is little functional deficit following transposition. However, without electrical stimulation it is unable to maintain the sustained contraction necessary to provide sphincteric function. This may explain the poor long-term results of the unstimulated graciloplasty in clinical practice[10–12]. The application of low-frequency electrical stimulation is known to convert fast-twitch skeletal muscle (such as the gracilis) into slow-twitch muscle ideally suited to prolonged contraction[13]. The application of electrical stimulation to the graciloplasty was pioneered at two centres, the Royal London Hospital in Whitechapel and Maastricht in the Netherlands[14–16]. Initial reports using the procedure to treat intractable acquired incontinence showed improvement in continence in 60–70 per cent of patients[17,18]. The technique has also been used successfully to treat incontinence arising from a congenital[19] or traumatic[20] aetiology. Use of the ESGN as part of anorectal reconstruction following abdominoperineal resection of the rectum has been less successful[21,22]. Subtle differences exist between centres in the method used to stimulate the transposed muscle. The London group prefers direct neural stimulation whereas the Dutch use intramuscular electrodes.

The aim of this study was to assess the efficacy of the ESGN in treating intractable incontinence using a standard protocol, incorporating direct neural stimulation, within a prospective multicentre trial.

Patients and methods

Patient details

All patients with severe incontinence secondary to sphincter trauma, neurogenic damage, anomalies of innervation or congenital anorectal anomalies were eligible for inclusion in the study. Patients with severe respiratory or cardiovascular co-morbidity, severe arthritis, malignant disease in the pelvis, previous perineal radiotherapy, a cardiac pacemaker, active perineal sepsis or known Crohn's disease were excluded. Patients were selected for the trial only if their incontinence was refractory to or not amenable to existing surgical techniques. All patients were considering a permanent stoma at the time of inclusion into the trial or had one already as the only way to control their symptoms. All patients were evaluated extensively, investigated and counselled before admission into the trial. The degree of incontinence was quantified using the Cleveland Clinic Florida 20-point incontinence scoring system (*Table 1*)[23]. Ethics committee approval was granted at a local level in the centres participating. All surgeons involved in the trial had visited the Royal London Hospital and had witnessed at least one procedure.

Between April 1993 and October 1996, 64 patients were entered into the trial (17 male and 47 female). The median age was 44·5 (range 15–76) years and the median length of follow-up was 16 (range 2–45) months. Patients were recruited from Cleveland Clinic Florida ($n = 15$), Royal Infirmary, Edinburgh ($n = 13$), Royal London Hospital, London ($n = 12$), St George's Hospital, Sydney ($n = 8$), Sahlgrenska Hospital, Gothenburg ($n = 7$), University of Naples ($n = 5$) and Queen Elizabeth Hospital, Birmingham ($n = 4$).

The patients formed a heterogeneous group with regard to the aetiology of the underlying incontinence. In the majority of patients incontinence arose as a result of direct sphincter disruption from obstetric injury ($n = 22$), iatrogenic damage ($n = 8$) or perineal trauma ($n = 6$). In 16 patients it was attributed to a denervated sphincter from pudendal neuropathy ($n = 10$) or a more proximal neurological deficit ($n = 6$). Seven patients had a congenital aetiology. In the remaining five incontinence followed restorative proctocolectomy ($n = 3$), congenital internal sphincter absence ($n = 1$) and isolated sphincter myopathy ($n = 1$).

Before entry into the study 75 per cent of the patients had undergone one or more (range 1–5) surgical procedures in an attempt to alleviate their incontinence; in the majority either a direct sphincter repair or a pelvic floor repair. In addition, 14 patients had a permanent stoma to manage their symptoms.

The operation was performed in stages and is described in detail elsewhere[24]. A preliminary vascular delay procedure was performed on the distal end of the gracilis muscle in 54 patients. In all but four of the patients a defunctioning stoma was either already present or was fashioned at this stage. Approximately 1 month later the patients were admitted for the second stage when the preprepared muscle was transposed around the anal canal. A custom-made electrode plate (Nice Technology, Fort Lauderdale, Florida, USA) was sutured over the main nerve and connected to the stimulator (Nice Technology Electrical). After the wounds had healed approximately 1 month after operation, stimulation was started and a period of muscle training begun.

Table 1 Cleveland Clinic Florida 20-point scoring system for faecal incontinence[23]

Nature of incontinence	Never	Rarely (< 1 per month)	Sometimes (< 1 per week ≥ 1 per month)	Usually (< 1 per day ≥ 1 per week)	Always (> 1 per day)
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Flatus	0	1	2	3	4
Wears pad	0	1	2	3	4
Altered lifestyle	0	1	2	3	4

0, Total continence; 20, total incontinence

Once completed, patients were readmitted for stage 3, closure of the covering stoma.

Physiological measurements and assessment of function were made before operation and at regular intervals after surgery.

Manometry was performed using a standard technique of anorectal manometry incorporating a water-filled microballoon, a water-perfused system or a solid-state transducer. The sensor was inserted into the anal canal and the pressure recorded at 1-cm stations from 0 to 5 cm from the anal verge, with the stimulator switched on and then off. Physiological measurements were made before operation, at the commencement of electrical stimulation and at regular intervals thereafter. Two measurements were made. Basal neosphincter pressure was defined as the pressure recorded at the site of the neosphincter with the stimulator switched off. Maximum neosphincter pressure (MNP) was the pressure recorded at the site of the neosphincter when the muscle was stimulated at tetanic frequencies and supramaximal voltages.

Statistical analysis

Paired data were compared using the Wilcoxon rank sum test.

Results

Morbidity

There was no perioperative death although three patients died during the course of the study, from causes unrelated to it, one from pancreatitis and two from malignancy. Following stage one there were 14 recorded complications. These included four saphenous nerve palsies, three cases of mild lymphoedema, four minor wound infections, one leg seroma, one parastomal hernia and one ileostomy fistula.

Following the second stage, despite the use of covering antibiotics, there were 24 infective complications in 22 patients. In ten this amounted to mild perineal or leg sepsis that resolved with antibiotics. In five perineal infection was associated with a degree of perineal wound breakdown and in three perineal debridement was necessary. In addition there were three proven episodes of deep venous thrombosis. Perioperative neuropraxia of the nerve to the gracilis occurred in three patients. This was only transient in two.

Physiological results

There was no statistical alteration in resting pressures before and after transposition. Anal canal occlusion pressures rose significantly, from a median maximum squeeze pressure before operation of 64 cmH_20 to a median MNP at the start of electrical stimulation of 140 cmH_20 ($P < 0.05$). The MNP declined during muscle training to a median value of 117 cmH_20 ($P < 0.05$) (*Table 2*).

Outcome

The outcome of patients 1 month after stoma closure is shown in *Fig. 1*. Fifty-five of the 64 patients had the stoma closed at the time of collating the data. The reasons for non-closure were death in two patients and incomplete muscle training in another five. These patients were excluded from subsequent analysis. In addition two patients did not undergo stoma closure because of technical failures including persistent neuropraxia in one and hardware sepsis in the other. Forty-four patients had the stoma closed and

Table 2 Anal canal pressures before and after surgery

Preoperative resting pressure (cmH_20)	40 (32–49)
Basal neosphincter pressure (cmH_20)	40 (34–46)
Preoperative maximum squeeze pressure (cmH_20)	64 (54–74)*
Maximum neosphincter pressure (cmH_20)	
At start of stimulation	140 (109–171)
At end of training	117 (96–138)*

Values are median (95 per cent confidence interval). $*P < 0.05$ *versus* maximum neosphincter pressure at the start of stimulation (Wilcoxon signed rank test)

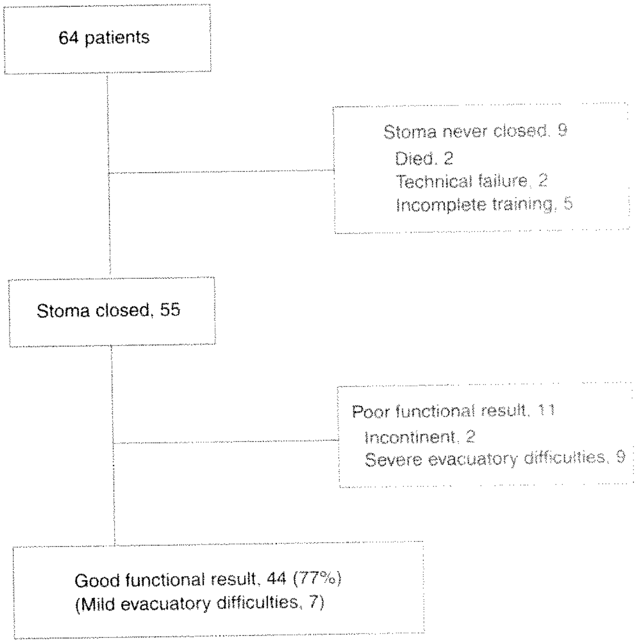
64 patients
Stoma never closed, 9
Died, 2
Technical failure, 2
Incomplete training, 5
Stoma closed, 55
Poor functional result, 11
Incontinent, 2
Severe evacuatory difficulties, 9
Good functional result, 44 (77%)
(Mild evacuatory difficulties, 7)

Fig. 1 Summary of functional outcome 1 month after stoma closure

experienced a good functional result (continent to solids) at 1 month. Including the two technical failures this represents a success rate of 77 per cent (i.e. 44 of 57 patients). This does, however, include seven patients who described moderate difficulty in evacuating (requiring regular suppositories or enemas). Eleven patients had a poor result at this stage either because of persistent incontinence or severe evacuatory difficulties. The mean Cleveland Clinic 20-point incontinence score decreased from 19 before operation to 6 1 month following surgery (*Fig. 2*).

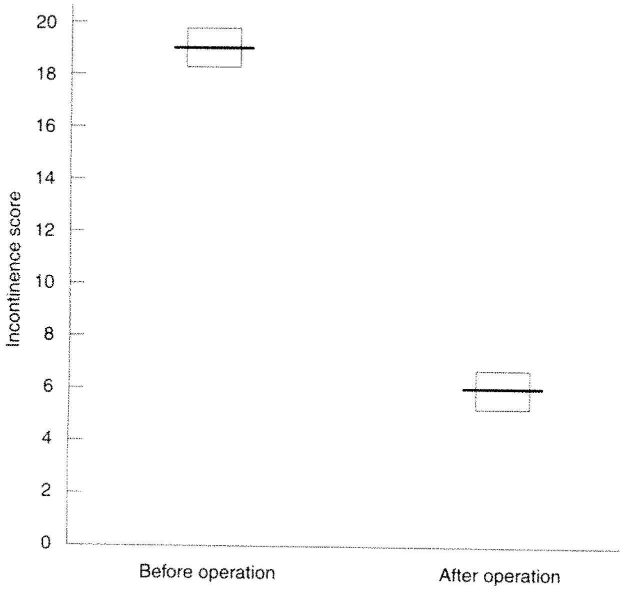

Fig. 2 Cleveland Clinic Florida 20-point incontinence scores before and 1 month after operation. Bars show mean values and boxes standard errors

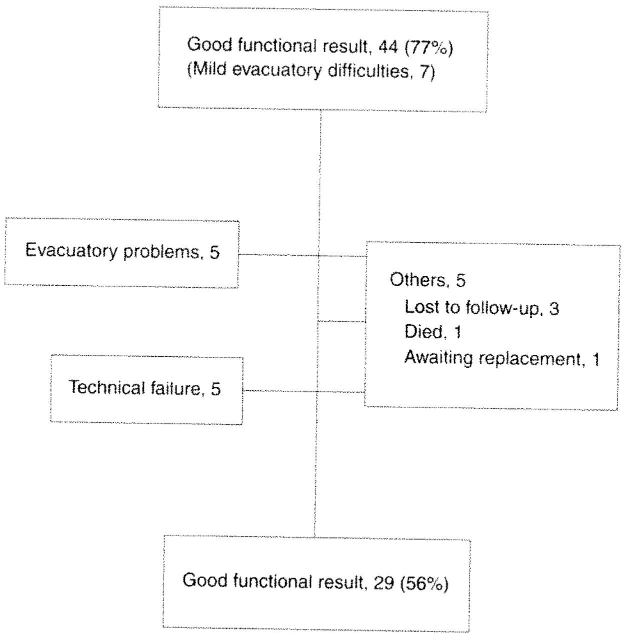

Fig. 3 Outcome of patients with a good initial result at the time of the last assessment, a median of 10 (range 1–35) months after stoma closure

At a median of 10 months following stoma closure, five of the seven patients who described mild to moderate evacuatory difficulties had deteriorated and required further surgery (a stoma in two and a colonic conduit in three) (*Fig. 3*). A further five patients experienced technical failure either as a result of repeated electrode plate migration ($n = 3$) or because of repeatedly depleted stimulators ($n = 2$). In a further five patients the functional outcome was unknown (three were lost to follow-up, one died and one was awaiting a replacement battery). Excluding these five patients, 56 per cent of patients (29 of 52) had a good functional outcome at a median of 10 months after stoma closure.

During the course of the study there were a number of hardware-related complications. There were 16 recorded episodes of plate migration or lead fracture in 11 patients which ultimately led to failure in four. Problems obtaining reliable replacement stimulators necessitated the use of a different device (Medtronic, Minneapolis, Minnesota, USA), connected to intramuscular electrodes. This was used in eight patients of whom seven have experienced a good result. In total there were 27 battery depletions in 21 patients. The median length of stimulator life in this study was 11 months.

Discussion

Historically the patient with incontinence refractory to surgical correction has resorted to a permanent stoma. The use of an unstimulated gracilis neosphincter provided encouraging results in the short term but proved less effective in the longer term. The addition of electrical stimulation not only provides a truly dynamic sphincter but also effects the phenotypic conversion of the muscle from type 2 (fast twitch) to type 1 (slow twitch), ideally suited for sphincteric function[25]. Results from the two pioneering centres using this technique revealed good results in approximately 65 per cent of patients[17,18]. This is the first report of a multicentre trial investigating the efficacy of this technique. A good functional outcome in 56 per cent of patients in this study at a median follow-up of 10 months is therefore encouraging.

It should be emphasized that the patients reported here formed a heterogeneous group. In some incontinence was the result of a primary motor defect of the anal sphincter alone. In others, however, including those with congenital incontinence, neurological damage and pudendal neuropathy, there was a combined motor and sensory deficit. The ESGN aimed to correct only the sphincteric deficit associated with incontinence. The Maastricht group reports lower success rates in patients with a congenital aetiology[19]. Similarly the results of the technique in total anorectal reconstruction following abdominoperineal excision of the rectum are less good[22]. Furthermore, the vast majority of patients operated on in this study had undergone previous perineal surgery which may have affected the contraction of the neosphincter and reduced anal compliance.

In this study, as in others, there was a high rate of perioperative complications[19,26,27]. This is likely to be related in part to the complexity of the technique and also to a learning curve effect. The high morbidity rate should be balanced against the realization that the only other option for these patients is a permanent stoma. Broadly speaking, complications can be grouped into three major categories: infective, technical and functional. Despite use of broad-spectrum antibiotics the infective complication rate following transposition and implantation of the electronic hardware was 34 per cent. This is higher than the 18 per cent reported by Baeten's group[26]. The Dutch report a much higher incidence of hardware sepsis (12 *versus* 5 per cent) but a considerably lower rate of perineal sepsis (3 *versus* 21 per cent). They use a different protocol, dispensing with the vascular delay stage and transposing the muscle 6 weeks before hardware implantation. The relatively high rate of perineal infection in the present study may relate to the high frequency of previous perineal surgery. Hardware sepsis is a disaster as it necessitates removal of the stimulator and/or the lead. Perineal sepsis alone is manageable and rarely spreads. However, its sequelae, particularly anal scarring and a reduction in anal compliance, can seriously affect the outcome. All of the patients in this study who developed moderate or severe perineal sepsis developed a degree of subsequent anal stenosis and difficulty in evacuation.

The major technical problems encountered were neuropraxia, electrode plate migration, fibrosis, and lead fracture and stimulator depletion. Direct neural stimulation utilizes an electrode plate placed directly over the main nerve to the gracilis and sutured into position. Direct neural stimulation ensures maximal motor unit recruitment and therefore maximizes neosphincter contraction. There is a risk of neuropraxia, although in two of three instances encountered in the present study reasonable function returned. Electrode plate migration, fibrosis or lead fracture, characterized by a marked increase in the threshold voltage of stimulation, occurred 16 times in 11 patients (17 per cent). It is difficult, using existing equipment, to differentiate between these entities and therefore it is necessary to replace the leads in all instances. Although this is usually possible, fibrosis around the nerve can make exact placement of the new lead difficult. An alternative is to use an intramuscular lead. A number of patients in this study ultimately received this form of stimulation with good effect. Direct muscle stimulation produces lower sphincteric closing pressures than neural stimulation[18]. The argument over which is the better form of stimulation could be resolved by a trial. The electrode plate used in the study is no longer produced but a modified neural lead is now available from another manufacturer (Medtronic) and initial experience suggests that problems with plate migration and lead fracture have been considerably reduced.

The length of stimulator life used in the study was very disappointing. Although mathematically predicted to survive 2–3 years they lasted a median of only 11 months. The stimulators used were prototypes modified from spinal cord stimulators and not previously tested in a clinical setting. The manufacturer of the hardware used in this study no longer exists. More reliable stimulators are now available (Medtronic). No problems with stimulator displacement were experienced in this study; in contrast, the Dutch group describe it occurring with a frequency of 9 per cent in their patients[26].

All the patients with a functioning neosphincter noticed an improvement in symptoms. Only two did not improve sufficiently to avoid a permanent stoma. The physiological data in this study mirror those of early reports and physiological studies on the technique[25]. The MNPs generated using direct neural stimulation are considerably higher than those reported using direct muscle stimulation where maximum pressures are of the order of 100 cmH_2O, approximately 60 per cent of that achieved in this study[18].

The major functional problem in these patients was of evacuatory difficulty. In all, 16 patients (25 per cent) experienced mild or moderate evacuatory difficulties that ultimately led to failure in 14. This problem is well documented following this procedure[26,28]. Its aetiology is not well understood but is likely to be multifactorial. Predisposing factors may include occult premorbid evacuatory difficulties, perineal sepsis and associated stenosis, previous perineal procedures and poor anal compliance[29].

Improvements in the resilience and longevity of the electronic hardware used, careful patient selection and efforts to overcome the evacuatory difficulties experienced by some will improve the long-term results. Determination of the effectiveness of this procedure as a durable and cost-effective alternative to a stoma requires longer-term follow-up.

Acknowledgements

The authors are grateful to the following who contributed to this study: I. Berndtsson, V. L. Billotti, D. Cheong, P. Esposito, A. Gonzales-Padron, M. L. Kennedy, J. Rius, A. Novi and T.-A. Teoh. B.J.M. was supported by a grant from the Wellcome Trust. N.S.W. was a consultant for NICE Technology between 1991 and 1995.

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Original article

Patients' perception of surgical services in a district general hospital

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Background: In addition to studying the outcomes of surgery in terms of mortality and morbidity rates and performance, it is also important to consider how patients perceive the delivery of the service given to them.

Methods: A patient satisfaction survey was carried out by the Surgical Epidemiology and Audit Unit of the Royal College of Surgeons of England, on patients undergoing surgical procedures by the Department of Surgery at Wrexham Maelor Hospital. No day cases were included in the study. Two hospitals in southern England (undergoing the same survey) designated X and Y were used for comparison.

Results: Some 2000 questionnaires were sent out twice; 1666 subjects (83 per cent) responded to the first questionnaire and 1445 (87 per cent) of these responded to a second questionnaire 6 weeks later (overall response 72 per cent). A total of 35 per cent of patients were older than 65 years of age. Some 76 per cent of patients with a malignant condition were seen within 4 weeks of referral compared with 38 per cent of those with a benign condition ($P < 0.0001$). A total of 78 per cent of patients with cancer were admitted within 4 weeks compared with 84 and 88 per cent in hospitals X and Y. Some 23 per cent of patients were admitted as an emergency. Eighteen per cent of patients did not know who presented a consent form to them before surgery compared with 13 and 17 per cent in hospitals X and Y ($P < 0.0001$). Some 26 per cent of patients perceived that they had complications after surgery compared with 27 and 25 per cent for hospitals X and Y. A total of 35 per cent of patients did not receive a follow-up appointment and 20 per cent of these patients were unhappy about this. Two areas of major concern revealed by the responses were the lack of written information and the overall poor scores generally attained by the emergency admission ward. However, 94 per cent of patients said that they would return to the same consultant.

Conclusion: Patients were generally happy with their surgical care and there was little difference between the three hospitals studied. Lower scores were given when patients were admitted to emergency admission wards. Higher scores were given when patients received printed information.

Paper accepted 13 July 1999

British Journal of Surgery 1999, 86, 1549–1555

Introduction

Irrespective of political initiatives such as the Patients' Charter, it is the duty of any medical practitioner to record and react to patients' experience of medical care. As well as studying the outcomes of surgery in terms of mortality and morbidity rates and performance, it is also important to look at 'customer satisfaction' of a given service. There has been a significant increase in consumerism and willingness (and ability) to criticize clinical services, but surgeons have recognized that some expectations of therapy can be unrealistic. The remit of this audit was to conduct an independent investigation of patients' experience of the quality of surgical care, including outcomes. The study was an anonymous, independent, postal questionnaire study.

Materials and methods

The Royal College of Surgeons of England Surgical Epidemiology and Audit Unit was funded by the Welsh

Office and the Wrexham Maelor Hospital Trust to undertake an independent review of the response of 2000 patients to surgery at Wrexham Maelor Hospital during the period July 1995 to April 1997. This hospital was one of 12 sites in which such audits took place between 1992 and 1998. Using patient feedback, these studies sought to examine the strengths and weaknesses of surgical service delivery across the entire treatment episode, from the first outpatient consultation to follow-up. The study looked at the strengths and deficits as perceived by the patients in order that these issues might be addressed. Comparative data were shown by two other hospitals undertaking a similar audit. The two comparative hospitals were district general hospitals in the south of England, designated X and Y for the purpose of this study. The three hospitals were chosen as they were able to provide the appropriate monies to finance their respective audits.

The questionnaire design used a variety of narrative questions and response options, using straightforward language that a patient might adopt when judging clinical services. An example of the questions is shown in *Fig. 1*. The study permitted simple measures of relative satisfaction with different core aspects of care. Scores were designed to allow interprofessional and interhospital comparisons.

The survey employed two different postal questionnaires. One was distributed immediately after hospital discharge and the second one 6 weeks after discharge. The questions generated both closed responses and free text answers. By encouraging free text responses, criticisms with a common theme might emerge. While acknowledging that such data were necessarily subjective and memory derived, staged distribution of the forms aimed to minimize the distortion from time lapse. However, it was apparent that patients' perspectives did change with time, as more patients were satisfied with the service when replying to the second questionnaire. The purpose of the second questionnaire was to assess any follow-up visits and/or complications that may have arisen since the initial questionnaire.

A very large sample size was used in this study to marginalize the overcompliant and overcritical patient. The survey was confidential in terms of patient, surgeon and hospital findings. The audits were unique because responses were analysed according to individual participating surgeons.

9 How would you rate the ward admission experience you had?

☐ The arrangements were very good, covering every need of the new patient

☐ The arrangements were acceptable, covering some but not all needs of the new patient

☐ The arrangements were rather poor, not covering the basic needs of the new patient

☐ I don't remember

Please add any comments you may have regarding improvements to the ward admission arrangements.

Fig. 1 Example of a question from the questionnaire

Statistical analysis

Standard (χ^2) tests of statistical significance and 95 per cent confidence intervals were used, where appropriate. In view of the very large numbers of patients studied, even though absolute differences in patient responses to the questions were small, they did reach statistical significance.

Patients' judgements of service quality were derived from certain 'rating' questions. It was necessary to render these responses numerically for the purposes of comparison. Overall percentage scores were drawn from aggregated responses/ratings on common themes. As most issues were given equal weight, the system allowed for the theoretical possibility of the 'perfect' surgical service.

As questions on the same service topic may have different ranges of response options, a composite scoring system was required to evaluate responses to several questions on the same aspect of the service. The solution was to recode the various available responses to the questions making up the survey so that they comprised equal parts of 100. In so doing, coding could be manipulated to deal with questions posing different orders of response, and the overall scores elicited by individual questions could be added together (*Table 1*).

For example if a consultant scored 63·6 per cent at very good recoded 100, 27·3 per cent average recoded 50 and 9·1 per cent poor recoded 0 for a particular question, the score for this question would be $(63{\cdot}6 \times 100) + (27{\cdot}3 \times 50) + (9{\cdot}1 \times 0)/100 = 77{\cdot}2$ per cent.

Although some issues were more within the control of the consultants concerned than others, the consultant scores created a benchmark against which they could be compared. A score of 80 per cent means that two of ten patients are less

Table 1 Scoring methodology

Value label	Value	Allocated score	Other possible scores	
Very good	1	100	100	100
Average	2	50	60	40
Poor	3	0	0	0

than satisfied with that aspect of the service. To add meaning to the numerical scoring system, clinicians were consulted during the pilot phase to agree a reasonable tripartite evaluation of 'good', 'acceptable' and 'poor' performances. Overall, a score of 85 per cent or greater was deemed to be 'good', 75–85 per cent 'acceptable' and below 75 per cent 'poor'.

Results

A total of 2000 questionnaires were mailed to patients. Some 1666 patients (83 per cent) responded to the first questionnaire. Of these, 1445 (87 per cent) responded to the second questionnaire, giving an overall two-questionnaire response rate from the original cohort of 72 per cent. There was an equal sex distribution. Approximately 60 per cent of patients were aged between 45 and 74 years, and 14 per cent were more than 75 years of age (*Fig. 2*). The distribution of diagnoses and the proportion of benign and malignant conditions is shown in *Fig. 3*. Digestive tract conditions included appendicectomy, cholecystectomy and anorectal conditions, thus diluting the proportion of malignant cases. The patients were equally divided between each of the four consultant surgeons (range 22–28 per cent patients per consultant).

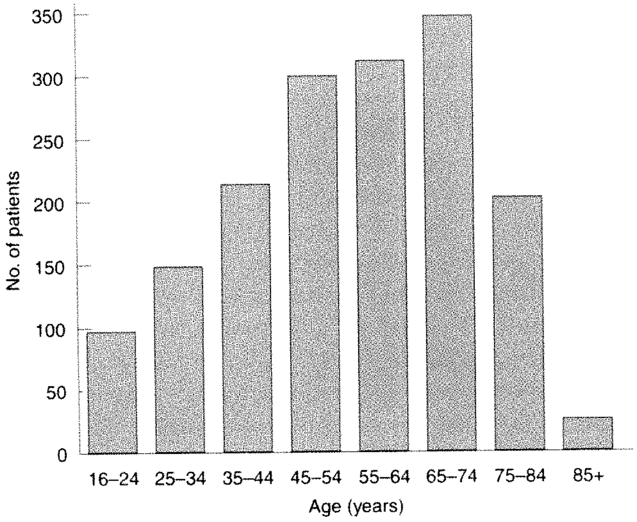

Fig. 2 Age distribution of the patients

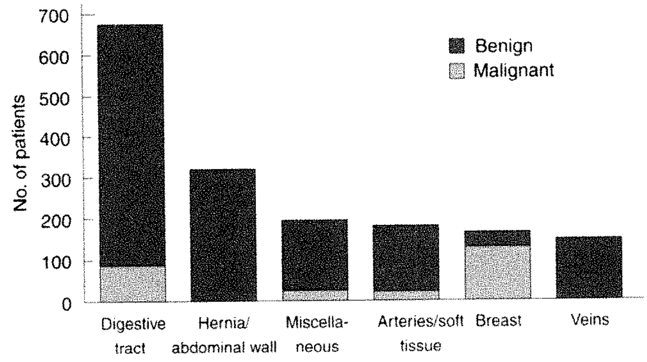

Fig. 3 Distribution of conditions and proportion of malignancies

Ward 1 is the emergency admission ward to which the majority of emergency patients are admitted, irrespective of condition. The remaining three wards contained elective general surgical patients each with a different specialty interest. Two of the four surgeons had expertise in upper gastrointestinal and breast surgery, and one each in colorectal and vascular surgery.

Outpatient/admission services

Some 76 per cent of patients with a malignant condition waited 4 weeks or less for an outpatient appointment after general practitioner (GP) referral compared with 61 and 81 per cent for hospitals X and Y respectively ($P < 0{\cdot}02$); 38 per cent of patients with a benign condition had a similar wait ($P < 0{\cdot}0001$). A total of 78 per cent of patients with a diagnosis of malignancy were admitted within 4 weeks compared with 84 and 88 per cent for X and Y. Some 59 per cent of patients were seen by the consultant at the first meeting compared with 71 and 49 per cent for X and Y ($P < 0{\cdot}0001$), but 69 per cent were seen by a nurse counsellor compared with 51 and 65 per cent respectively ($P < 0{\cdot}0005$). For all patients the cancellation rate (appointment cancelled) was 23 per cent compared with 14 and 16 per cent respectively ($P < 0{\cdot}0001$). There were 29 critical comments made, 18 regarding organization, two because of inadequate time, seven related to a doctor's attitude and two commenting on the inexperience of the doctor. The consultant variables for the outpatient/admission responses are shown in *Table 2*.

Inpatient stay

In Wrexham 23 per cent of patients were admitted as an emergency compared with 17 per cent in hospital X and 14 per cent in hospital Y; 73 per cent thought that the admission arrangements were good compared with 63 per cent for both X and Y. Of 66 critical comments about the admission, 23 related to delay in finding a bed, 13 to organizational difficulties, 11 to poor communication, seven to lack of information, five to nursing attitudes, four to lack of privacy and there were three inappropriate comments. Some 13 per cent of admissions were postponed compared with 11 and 13 per cent in X and Y.

The consent form was presented by any grade of surgeon in 69 per cent of patients, by a ward nurse in 15 per cent and

Table 2 Consultant variables for initial outpatient visit

	Consultant				
	1	2	3	4	P*
Waiting time for admission					—
Within 4/52	169 (46)	115 (41)	87 (37)	101 (34)	
Wait > 1 year	11 (3)	48 (17)	28 (12)	12 (4)	
Waiting time in clinic					< 0·002
< 30 min	194 (54)	121 (47)	102 (47)	134 (47)	
> 60 min	24 (7)	40 (16)	38 (18)	37 (13)	
Effort to communicate					< 0·0001
Every effort	319 (83)	224 (76)	174 (69)	265 (83)	
Not enough effort	12 (3)	9 (3)	14 (6)	12 (4)	
Time made available for discussion					< 0·003
Plenty of time	324 (89)	234 (86)	184 (79)	271 (88)	
Not enough time	40 (11)	38 (14)	49 (21)	36 (12)	
Printed information from consultant					< 0·0001
Yes	55 (13)	37 (10)	39 (12)	91 (25)	
No	364 (87)	334 (90)	291 (88)	275 (75)	

Values in parentheses are percentages. *χ^2 test

in 16 per cent the respondent did not know. In hospital X the corresponding figures were 69, 18 and 13 per cent, and in Y 55, 28 and 17 per cent ($P < 0{\cdot}0001$). The anaesthetist visited the patient before 82 per cent of operations compared with 97 and 74 per cent in X and Y ($P < 0{\cdot}0001$). There was variation in preoperative visiting; consultant 1 saw 65 per cent of patients in hospital before operation compared with 59 per cent for consultant 2, 55 per cent for consultant 3 and 52 per cent for consultant 4 ($P < 0{\cdot}005$). The ward variations for the different aspects of the inpatient stay are summarized in *Fig. 4*. Of 38 critical comments made, 95 per cent were a consequence of lack of information given after operation.

Follow-up/outpatient visit

Overall, 65 per cent of patients had an outpatient follow-up visit arranged (72 and 64 per cent for X and Y; $P < 0{\cdot}0002$) and, of those seen, 84 per cent were happy with the outcome of the visit (86 and 83 per cent for X and Y). There was considerable variation between surgeons and the feelings of the patient regarding follow-up (*Table 3*). Of patients not seen routinely as outpatients (e.g. after hernia repair, cholecystectomy, non-specific abdominal pain, etc.) 20 per cent would have preferred a follow-up appointment.

Perceived outcome and complications

Overall, 26 per cent of patients said that they had suffered some form of complication as a consequence of surgery (27 and 25 per cent in X and Y). The rate of complications perceived by patients after operation by consultants 1–4 was 19, 30, 27 and 29 per cent respectively ($P < 0{\cdot}003$). Nine per cent of patients required a second operation, 15 per cent required other hospital treatment, 34 per cent were treated by the GP, 25 per cent required no further treatment and in 16 per cent there was an uncertain response.

In general 78 per cent of all respondents were happy overall with the appearance of their wounds (78 and 73 per cent for X and Y; $P < 0{\cdot}0006$).

Over 90 per cent of patients felt their consultant was as involved as they wished and more than 94 per cent of patients would return to the same consultant for any other treatment. Of 1071 patients who were originally worried about their condition, 55 per cent felt all their worries had been resolved, 37 per cent still had some slight concerns regarding the outcome and 8 per cent remained as worried as before the operation.

Staffing

There were several questions for Wrexham regarding staffing levels within the hospital. Responses revealed that 82 per cent of patients felt that the hospital had enough doctors but only 67 per cent felt that there were enough nurses. This was reflected in the critical comments as 53 respondents complained of nursing shortages or delay, seven of doctor shortages or delay and five a combination of nurse/doctor shortages or delays.

Overall comparisons

When the four consultants were compared regarding outpatient and inpatient variables the scores were 84·8,

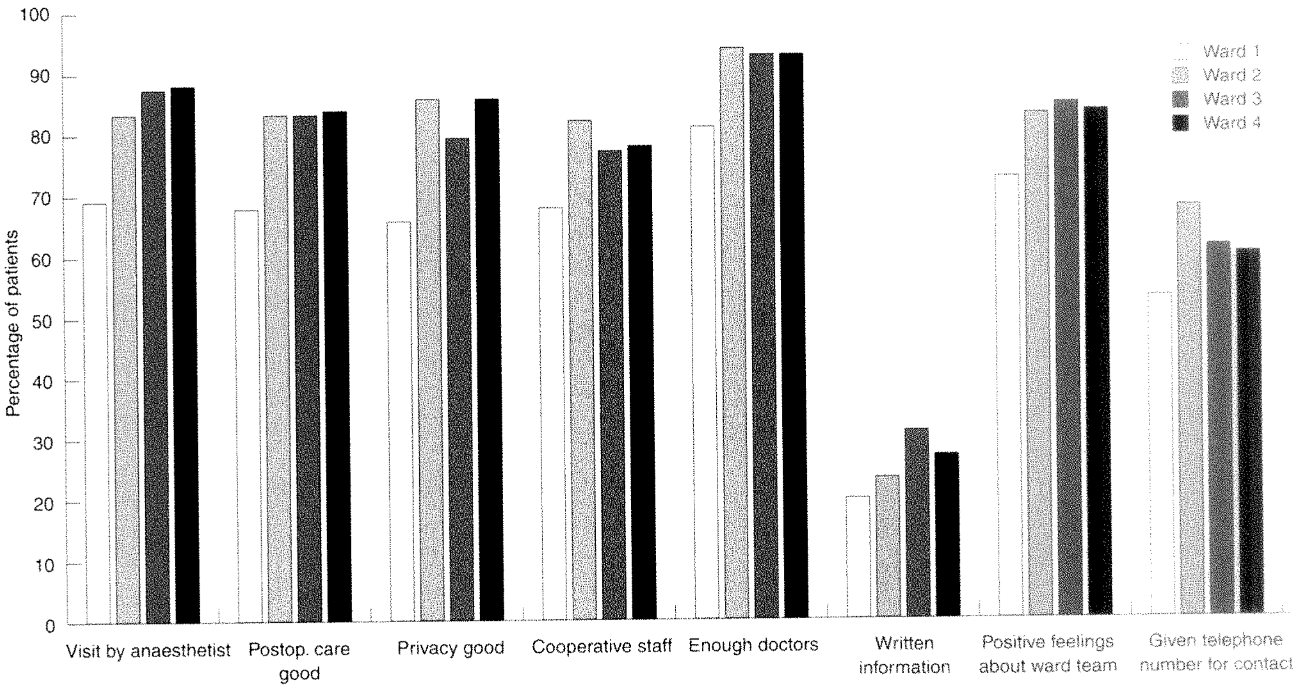

Fig. 4 Ward variations for inpatient stay

Table 3 Consultant variation according to postoperative outpatient visit

	Consultant				
	1	2	3	4	P^*
No. of patients not offered an outpatient visit who thought they needed one	23 (20)	33 (29)	32 (43)	33 (30)	< 0·007
No. of patients who saw consultant at outpatient visit	95 (42)	98 (49)	98 (59)	98 (56)	< 0·0007

Values in parentheses are percentages. $^*\chi^2$ test

81·3, 76·3 and 82·0 per cent respectively, for surgeons 1–4 with a mean of 81·1 per cent.

The overall ward scores were 80·4, 91·0, 89·5 and 90·3 per cent for wards 1–4 with a mean of 87·8 per cent. Ward 1 consistently underperformed in the patients' view for most variables.

When the hospitals were compared overall, Wrexham scored 71·3 per cent, hospital X 71·7 per cent and hospital Y 71·9 per cent, demonstrating clearly that there was no difference between the hospitals, as perceived by the populations studied.

Discussion

The Patient Satisfaction Survey was developed and administered by the Surgical Epidemiology and Audit Unit of the Royal College of Surgeons of England[1]. As an independent study it aimed to avoid the risk of bias of studies conducted by clinicians or hospitals on their own patients[2]. An independent study also guaranteed the confidentiality and anonymity of the respondents and participating surgeons. The ability of patients to make comments separate from the questions answered has previously been emphasized as very important by Dull *et al.*[3] and Lund[4].

In comparison to hospitals X and Y, Wrexham had significantly more patients admitted as an emergency. The relatively lower proportion of emergency admissions than expected was explained by the fact that the patients were a random selection of the admissions.

In the outpatient department, patients with malignant conditions were seen relatively quickly, demonstrating prioritization of patients before admission. The percentage of patients admitted within 4 weeks was less in Wrexham than in hospitals X and Y. Contributing factors included the high cancellation rate in Wrexham of 23 per cent, and the high and increasing rate of emergency admissions, over which the consultants had little or no control. The main difference between consultant scores in the outpatient clinic related to the delivery of printed information for patients undergoing varicose vein surgery. It was apparent from the survey that patients appreciated such printed information, as has been emphasized previously[5,6].

The majority of patients were happy with their admission arrangements, although patients expect to be admitted straight to a bed without delay. Poor communication was also highlighted in the critical comments. The percentage of patients receiving a preoperative visit in hospital by the surgeon (range 52–65 per cent) was a cause for concern, as was the 33 per cent of patients who had their consent form presented by a nurse or an unknown person. Recent recommendations by the General Medical Council state that consent should be obtained by the person undertaking the procedure or a delegate who is deemed suitably trained and qualified, has knowledge of the procedure and acts in accordance with the guidance as stated. These guidelines had not been published at the time of the survey. It is of concern that patients believed that a nurse presented the consent form, although it is possible that there was confusion about female medical staff. There was no nurse-practitioner in post at the time of the survey. Of even greater concern were the 18 per cent of patients who did not know who presented the consent form. This would suggest a lack of communication between the medical staff and patient; good communication is a prerequisite to informed consent. These results are at variance, however, with the 80 per cent of patients who stated that they had received full information regarding their operation. This rate compares well with the 74 per cent reported by Cohen *et al.*[7], although that study looked at hospital-based care in general. There was also room for improvement on preoperative visits by the anaesthetist.

Of patients not offered routine outpatient follow-up, 20 per cent felt that they would have benefited from an appointment, despite explanation that it was unnecessary. This demonstrated the differing expectations of outpatient follow-up between surgeon and patient. The complication rate perceived by the patients for each surgeon varied considerably. Whether this was due to the amount of information given about an operation, i.e. if a particular occurrence was mentioned the patient did not consider it to be a complication, is impossible to elucidate. Of patients with a complication, only 24 per cent required subsequent hospital treatment; the majority were managed by the GP or required no additional intervention. Ultimately 78 per cent of patients were happy with the appearance of the wound (generally the only visible sign of an operation).

Overall there was little variation between consultants, such that they all delivered a similar standard of care irrespective of specialist interest. There was also minimal difference in overall scores between the three hospitals.

In Wrexham the most significant and consistent difference in patient response, compared with hospitals X and Y, was the patients' perspective of the emergency admissions ward (ward 1). In general it was felt that there were not enough staff, communication was sometimes poor, and patients had to wait an excessive length of time to be seen by the admitting staff. The medical staff also had responsibility for routine work away from the emergency ward, putting a strain on time available to deal with emergency patients. This perspective was in direct conflict with the views of the medical staff who felt that concentrating emergency patients in a single area not only improved the quality of medical and nursing care, but was also justified on the basis of risk management.

This study demonstrated that, in the patients' view, the three National Health Service hospitals studied delivered broadly similar care. Patients looked less favourably on the emergency admission ward in Wrexham, but did like to receive printed information about their condition[8]. This survey was of value, not only in providing an overall measure of care as perceived by patients but also in suggesting improvements to be made in written communication to patients and staffing of the emergency admission ward. The targeting of resources to surgical services in order to increase specialist care and minimize delay is warranted.

The information obtained from satisfaction surveys can be used in different ways by different groups within the hospital establishment. However, extreme care must be exercised. An improvement in patient satisfaction may not necessarily correspond to an improvement in health care.

Acknowledgements

Financial support was obtained from The Welsh Office and Wrexham Maelor NHS Trust.

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Original article

Prognosis after breast recurrence following conservative surgery and radiotherapy in patients with node-negative breast cancer

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Background: Breast conservation surgery with radiotherapy is a safe and effective alternative to mastectomy for early-stage breast cancer. This retrospective study examined the outcome of patients with isolated local recurrence following conservative surgery and radiotherapy in node-negative breast cancer.

Methods: Between November 1979 and December 1994, 503 women with node-negative breast cancer were treated by conservation surgery and radiotherapy without adjuvant systemic therapy.

Results: After a median follow-up of 73 months the 5-year rate of freedom from local recurrence was 94 per cent. Thirty-five patients developed an isolated local recurrence within the breast as a first event. Thirty-three patients were treated with salvage mastectomy and two patients were treated with systemic therapy alone. The 5-year rate of freedom from second relapse was 46 per cent and the overall 5-year survival rate was 59 per cent for patients who had salvage mastectomy. Patients who developed breast recurrence as a first event had a 3·25 greater risk of developing distant metastasis ($P < 0{\cdot}001$) than those who did not have breast recurrence as a first event.

Conclusion: Salvage mastectomy after local recurrence was an appropriate treatment if there was no evidence of distant metastasis. Breast recurrence after conservative surgery and radiotherapy in node-negative breast cancer predicted an increased risk of distant relapse.

Paper accepted 20 June 1999

British Journal of Surgery 1999, **86**, 1556–1562

Introduction

Large randomized trials have shown equivalent survival, stage for stage, for patients with breast cancer treated with conservative surgery and radiation therapy compared with total mastectomy and axillary dissection[1–5]. However, patients remain at risk for breast recurrence. The incidence of breast recurrence ranges from 5 to 10 per cent at 5 years and some series suggest that patients may be at persistent, although low, risk of local recurrence even after 10 years[6–9].

The impact of local recurrence on prognosis is less well defined. It is confounded by a competing risk of distant relapse that is higher for patients with adverse pathological features of the primary tumour, such as large tumour size or node positivity. Following breast recurrence, salvage mastectomy is usually considered if there is no evidence of distant disease. The results of salvage surgery have varied widely with the 5-year survival rate ranging from 48 to 84 per cent[10–15]. Several studies have suggested a relatively good prognosis after salvage mastectomy, whereas others have suggested breast recurrence to be a marker of risk rather than a cause of distant metastasis[16–19]. A few studies have examined the impact of breast recurrence in node-negative breast cancer where there is a low competing risk of distant relapse. These studies have suggested that patients in whom local recurrence follows conservative surgery and radiotherapy are at increased risk of developing distant metastasis[20,21].

The present study reports on a group of patients who developed breast recurrence after conservative surgery and radiotherapy. The aim of the study was to assess the likelihood of further relapse in patients whose original breast cancer was node negative.

Patients and methods

Between November 1979 and December 1994, 1162 patients had conservative surgery and radiotherapy for breast cancer at Westmead Hospital. Five hundred and sixty-three women had a negative axillary dissection, with at least five nodes removed. Axillary dissection was not performed routinely for older postmenopausal women who received axillary radiation. The study population consisted of 503 of these women who received no adjuvant systemic therapy. Women with non-invasive ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ*, bilateral breast malignancy and patients with a significant previous malignancy were excluded from the present study.

The median age at diagnosis was 48 (range 22–89) years. Two hundred and forty-two patients (48 per cent) were premenopausal, 164 (33 per cent) were postmenopausal and 41 (8 per cent) were perimenopausal at diagnosis. Preoperative mammography had been performed in 428 patients (85 per cent). Patients who did not have a mammogram were treated predominantly in the early 1980s at smaller district hospitals. The investigations used to provide the initial diagnosis of malignancy included a fine-needle biopsy in 180 patients (36 per cent), incisional biopsy in 16 (3 per cent) and a definitive lumpectomy in 307 (61 per cent). A separate re-excision of the primary site was undertaken in 26 per cent of patients.

Surgical and radiotherapy techniques have been addressed elsewhere[6]. All patients received whole breast irradiation using tangential wedge-corrected fields with no bolus to a median 46 (range 40–54) Gy by 6-MeV photons over 6 weeks. A boost to the primary site was given to 421 patients (84 per cent). The boost was delivered by iridium-129 implant in 109 patients and electron therapy in 312. The median dose was 16 (range 10–30) Gy.

Minimum follow-up data were obtained to 1 January 1997. Follow-up duration was calculated from the date of first treatment (surgery) to the date of last follow-up, or death. The median follow-up, based on censoring distribution, was 73 months[22]. Twenty-two patients were lost to follow-up without evidence of breast recurrence; one of these patients developed distant metastasis.

Breast recurrence was defined as the reappearance of carcinoma in the treated breast and was scored if it occurred alone, before, or simultaneously with, distant relapse. In this study, two patients developed breast recurrence after distant relapse and one patient developed simultaneous breast recurrence and distant relapse; all three patients were excluded from further analyses of patients with isolated local recurrence. Predictors of breast recurrence have been reported previously[6]. The site of recurrence was classified according to its location in the breast[7]. 'True recurrences' were recurrences that occurred within the area of the boost; 'marginal misses' were recurrences that occurred up to 2 cm from the boost area; 'recurrence elsewhere' occurred in other quadrants of the breast; 'skin recurrences' were recurrences that were confined to the skin and involved no underlying mass; and 'diffuse recurrence' involved the whole breast. In women who received no boost, a 'true recurrence' was classified as recurrence that occurred within the quadrant described in the initial history, clinical examination findings and/or investigations.

Breast recurrence was confirmed by fine-needle aspiration or excision biopsy. After recurrence, patients were investigated with full blood count, liver function tests and chest radiography. If there were symptoms or abnormalities of blood tests to suggest metastatic disease, a bone scan and liver ultrasonography were performed. 'Distant relapse' was defined as relapse at a site other than the breast or chest wall. 'Freedom from second relapse' after breast recurrence was defined as survival without further local recurrence, nodal recurrence or distant metastasis. This study was restricted to patients with node-negative breast cancer in order to measure breast recurrence and the freedom from second relapse in a cohort in which the recurrence rates would be less influenced by the competing risk of distant relapse or the influence of chemotherapy. No patient developed disease recurrence in the axilla.

Overall survival was calculated by considering death from any cause as an event. Freedom from breast recurrence, freedom from second relapse and overall survival were calculated by the method of Kaplan and Meier[23]. The factors with potential prognostic value after breast recurrence included age at diagnosis of the primary tumour, site of recurrence, disease-free interval and mode of detection. In this assessment, age less than or equal to 34 years was used as a cut-off because many studies consider this age group as young in relation to breast-conserving treatment after a diagnosis of breast carcinoma[24–26]. A disease-free interval of 39 months was used a cut-off because this was the median time to breast recurrence.

The hazard ratio for the development of distant metastasis was calculated for patients with breast recurrence as a first event with respect to those who did not have such recurrence as a first event. The separation of patients into groups according whether or not they developed breast recurrence could lead to biased results if standard methods, such as the log rank test, were applied. This analysis used time-dependent Cox proportional hazards models (Mantel–Byar method) with a time division at 18 months. This interval allowed all patients in the comparison adequate exposure time to develop distant metastasis (the first breast recurrence occurred at 9 months). Unlike a landmark analysis, the proportional hazards approach allowed for the adjustment of baseline prognostic factors[27]. The baseline prognostic factors considered were tumour stage (T_2 *versus* T_1), age (continuous) at diagnosis and oestrogen receptor status.

Results

The clinical and pathological characteristics of the 503 node-negative patients with breast cancer are shown in *Table 1*. The 5- and 10-year rates of freedom from local recurrence were 94 and 87 per cent respectively (*Fig. 1*).

Table 1 Characteristics of 503 patients with axillary node-negative breast cancer

	No. of patients
Age at diagnosis (years)	
≤ 34	37 (7)
35–40	59 (12)
41–49	188 (37)
≥ 50	219 (44)
Median age (years)	48
Mode of detection	
Breast symptoms	390 (78)
Clinical examination	24 (5)
Mammographic screening	89 (18)
Clinical T stage	
T_1	368 (73)
T_2	133 (26)
T_3	2 (0)
Oestrogen receptor status	
Positive	149 (30)
Negative	88 (17)
Unknown	266 (53)

Values in parentheses are percentages

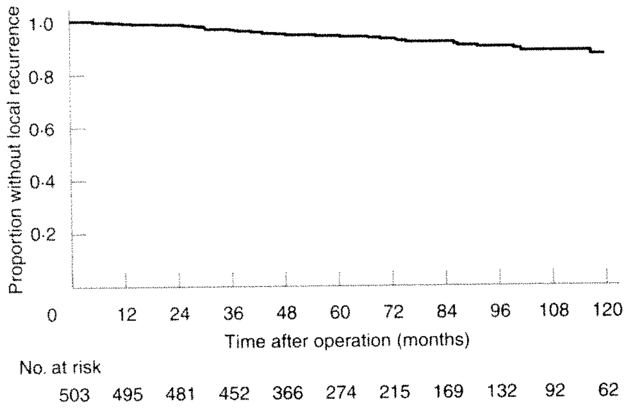

Fig. 1 Freedom from local recurrence for 503 patients with node-negative breast cancer. This figure includes two patients who developed local recurrence after distant relapse and one who developed simultaneous local recurrence and distant relapse

Thirty-five patients (7 per cent) developed isolated breast recurrence; the clinical and pathological characteristics of these patients are shown in *Table 2*. The median age of this group was 41 years compared with 48 years for the 503 patients. Twenty-four of the breast recurrences were first detected by physical examination and 11 by routine follow-up mammography.

The median time to breast recurrence was 39 months. The most common site of recurrence was at the primary site, with a median time to recurrence of 39 (range 12–117) months. Seven of 35 recurrences occurred elsewhere in the breast after a median interval of 55 (range 9–101) months. There were three patients with diffuse recurrence and none with a skin recurrence. Thirty-one patients had an invasive carcinoma at recurrence and four had DCIS.

The management of patients after breast recurrence is shown in *Table 2*. The use of systemic therapy at the time of recurrence was at the discretion of the treating physician. Salvage mastectomy was performed in 33 of the 35 patients. In addition, eight patients received chemotherapy after breast recurrence and 11 received tamoxifen. One patient received chemotherapy and one patient received tamoxifen as the sole therapy for local recurrence.

Table 2 Characteristics and main salvage therapy of 35 patients who developed isolated breast recurrence

	No. of patients
Age at initial diagnosis (years)	
≤ 34	9
35–40	6
41–49	15
≥ 50	5
Median age at diagnosis (years)	41
Clinical T stage at initial presentation	
T_1	26
T_2	9
Oestrogen receptor status at initial diagnosis	
Positive	11
Negative	9
Unknown	15
Mode of detection at recurrence	
Clinical examination	24
Mammogram	11
Pathology at recurrence	
Invasive carcinoma	31
DCIS	4
Salvage therapy	
Mastectomy	18
Mastectomy + chemotherapy*	4
Mastectomy + chemotherapy + tamoxifen	4
Mastectomy + tamoxifen	7
Chemotherapy	1
Tamoxifen	1

DCIS, ductal carcinoma *in situ*. *Three patients received chemotherapy before mastectomy

The 5-year actuarial rate of freedom from second relapse after salvage mastectomy was 46 per cent (*Fig. 2*). There was a higher rate of further relapse after salvage mastectomy in patients aged under 34 years at diagnosis, when breast recurrence was detected clinically and when the disease-free interval was less than 39 months. Seven of 18 patients who developed breast recurrence within 39 months remain disease free compared with 11 of 17 who developed a later recurrence (*Table 3*). The overall 5-year survival rate after salvage mastectomy was 59 per cent.

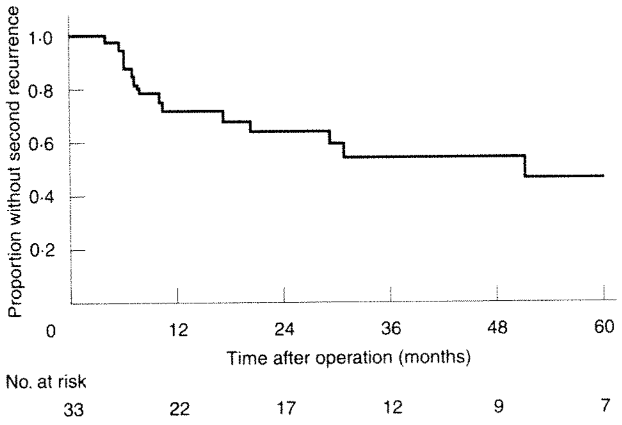

Fig. 2 Freedom from second relapse following salvage mastectomy in 33 patients

Table 3 Factors associated with second relapse after isolated breast recurrence in 35 patients

	No. of patients with no evidence of disease
Age (years)	
≤34	2 of 9
>34	16 of 26
Site of recurrence	
True recurrence or marginal miss	15 of 25
Elsewhere in the breast	3 of 7
Diffuse	0 of 3
Disease-free interval (months)	
≤39	7 of 18
>39	11 of 17
Mode of detection	
Clinical examination	11 of 24
Mammogram	7 of 11

Table 4 Time-dependent Cox regression analysis with the end-point as time to a distant relapse

Factor	Hazard ratio	*P*
T stage*	1·75 (1·08–2·82)	0·03
Age at diagnosis†	0·97 (0·95–0·99)	0·02
Breast recurrence‡	3·25 (1·72–6·15)	<0·001

Values in parentheses are 95 per cent confidence intervals. *T_2 or higher compared with T_1; †reduction in hazard for each year of increase in age at diagnosis of original breast cancer; ‡breast recurrence as a first event

The disease status at last follow-up or death for the patients who developed local recurrence was as follows: 18 patients remain disease free, 15 have developed distant relapse and two have chest wall disease as the sole site of relapse. Of the 467 patients who did not have breast recurrence as a first event, 56 (12 per cent) have developed distant relapse. Patients who developed breast recurrence as a first event had a 3·25 (95 per cent confidence interval 1·72–6·15) greater risk of developing distant metastasis ($P < 0{\cdot}001$) (*Table 4*).

Discussion

Conservation surgery with radiotherapy is widely accepted as appropriate treatment for most patients with early-stage breast cancer. The risk of breast recurrence is approximately 5–10 per cent at 5 years but patients will continue to have a low risk of such recurrence after this time[6–9]. The impact of breast recurrence on survival has been debated. The breast recurrence rate reported here after breast conservation is similar to that of other series and, after salvage mastectomy, 46 per cent of patients remained disease free at 5 years[1,11,13,20,28]. The present study suggests that, although patients with breast recurrence are at high risk of developing further relapse, salvage mastectomy is appropriate if there is no evidence of metastasis at recurrence.

In the present study, 11 of 35 breast recurrences were detected by mammography. These patients had a better disease-free survival rate after breast recurrence than those whose recurrence was detected clinically. Mammography can detect a recurrent tumour when it is smaller. Some recurrences will be predominantly DCIS which has a good prognosis and is more likely to be detected mammographically than clinically[13]. Four of the patients in this study had DCIS at recurrence, all of whom remained disease free at last follow-up.

In this study, 25 (71 per cent) of 35 breast recurrences were at the primary site, which is consistent with other series in which the rate of breast recurrence at or near the primary site has ranged from 67 to 86 per cent[7,8,10,12,14]. In common with other series, the median delay to breast recurrence was shorter in patients who developed recurrence at the primary site (39 months) than in patients who developed recurrence elsewhere in the breast (55 months). It has been explained previously that failures at the primary site indicate recurrence of the original tumour whereas recurrence elsewhere is thought to represent either subclinical disease at the time of initial treatment or a new tumour[7]. Kurtz *et al.*[8] suggested that patients who developed recurrence elsewhere in the treated breast may have a more favourable outcome.

The majority of patients who develop breast recurrence will be operable. In the series by Fowble *et al.*[12] the rate of simultaneous or antecedent metastasis among 65 patients who developed breast recurrence was 14 per cent. Similarly, in a series by Abner *et al.*[13] the rate of simultaneous distant metastasis was 7 per cent among 166 patients who developed breast recurrence. The reported rate of simultaneous metastasis depends on the extent of investigation at the time of recurrence. The reported 5-year survival rates after salvage mastectomy range from 48 to 84 per cent[10–15]. The 5-year survival rate of 59 per cent after salvage mastectomy in the present study is consistent with these reports.

The main factors associated with prognosis after breast recurrence are the size of the recurrent tumour, pattern of recurrence and disease-free interval. Diffuse recurrence within the breast, recurrence involving the skin and that involving the breast and axilla are reported to have poor outcomes[10,14,18,29]. Less than 25 per cent of patients who develop breast recurrence will have a diffuse recurrence, although various definitions of diffuse recurrence have been applied in previous studies. Three of the present patients developed diffuse recurrence and a further distant relapse.

Previous studies have shown that patients who develop breast recurrence after a short disease-free interval have a poorer prognosis than patients who develop a late recurrence. In a study by Haffty *et al.*[28] the rate of distant metastasis was 50 per cent for patients who developed breast recurrence within 4 years compared with 17 per cent for patients who developed recurrence after 4 years ($P < 0 \cdot 01$). The 5-year survival rates in the two groups were 50 and 78 per cent respectively ($P < 0 \cdot 05$). Similarly, in a study by Fourquet *et al.*[11], of 56 patients who developed breast recurrence after conservative surgery and radiotherapy, the 5-year actuarial survival rate was 44 per cent for patients who developed recurrence within 3 years compared with 87 per cent after 3 years. In the present study, ten (56 per cent) of 18 patients who developed breast recurrence within the median time of 39 months developed a distant metastasis compared with five (29 per cent) of 17 patients who developed recurrence after 39 months.

The present study included node-negative patients because this group has a low competing risk of distant disease. None of these patients received systemic therapy with the initial treatment; if breast recurrence predicts an increased risk of distant metastasis, then systemic therapy at the time of relapse may be beneficial. In another study of node-negative breast cancer reported by Whelan *et al.*[20] early breast recurrence was associated with a poorer prognosis and a higher risk of distant metastasis. Whether breast recurrence is a cause of, or a marker for, risk of distant metastasis has been debated. Fisher *et al.*[19] concluded from the National Surgical Adjuvant Breast Project B-06 trial that breast recurrence is a marker for risk of distant metastasis but not a cause. Veronesi *et al.*[30] analysed the pattern of relapse in women treated with quadrantectomy, axillary dissection and radiotherapy at the Milan Cancer Institute and concluded that breast recurrence and distant metastasis are partially independent events. They also found that women with breast recurrence have a greater risk of distant metastasis, especially if the recurrence occurred within 2 years of initial treatment.

Mastectomy is the treatment of choice for breast recurrence although some centres have used wide local excision for small, well circumscribed recurrences[8]. In a series by Kurtz and Spitalier[31] the subsequent locoregional failure rate was 36 per cent at 5 years after wide local excision for breast recurrence. Wide local excision may be associated with poor cosmesis if a large excision is required to obtain clear margins. The surgical margins after breast recurrence can be difficult to assess. Fowble *et al.*[12] were unable to identify any pathological factors that would predict a localized recurrence.

Total mastectomy for breast recurrence yields optimal local control. The irradiated breast is more oedematous and fibrotic; tissue planes such as pectoral fascia are less yielding. Resection needs to be carried out to healthy margins and skin flaps should be planned carefully. Despite the higher possibility of wound complications in irradiated tissue, primary healing tends not to be a problem[32]. When large amounts of breast skin must be excised for diffuse recurrence or skin involvement, the muscle bed may require split skin grafting. A deep and large defect may require a muscle flap repair.

In conclusion, breast recurrence after conservative surgery and radiotherapy in patients with node-negative breast cancer predicted a greater risk of distant relapse compared with that in patients without breast recurrence. If investigations suggested no evidence of distant metastasis, salvage mastectomy was the appropriate treatment. Extensive local or diffuse recurrence and a short disease-free interval predicted a greater risk of further relapse. Ideally, these patients should be considered for systemic therapy but as yet there are few prospective data to support this approach.

Acknowledgements

The authors thank Dr Anna Rangan and Ms Joanne Stubbs for statistical advice and Dr Greg Heard for editorial comment.

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Endoscopically assisted, minimally invasive parathyroidectomy

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Background: Despite the success of open parathyroid exploration, minimally invasive alternatives have been emerging. This study reports an experience with endoscopically assisted, minimally invasive parathyroidectomy and evaluates its current role in patients undergoing surgery for hyperparathyroidism.

Methods: One hundred consecutive patients requiring surgery for hyperparathyroidism were evaluated. Endoscopic parathyroidectomy was offered based on the absence of coexisting nodular thyroid disease, previous neck surgery or irradiation, suspicion of parathyroid hyperplasia, or other anatomical or medical contraindications. Some 24 of 100 patients fulfilled the criteria and underwent endoscopic parathyroidectomy. Unequivocal localization to a single site by a technetium-99m-radiolabelled sestamibi scan allowed removal of the adenoma through a 25-mm suprasternal incision while being guided by a surgical telescope.

Results: There were no statistically significant differences in operating time or the mean size of resected adenomas between patients undergoing endoscopic and open parathyroidectomy. Four patients required conversion to an open procedure. Two patients developed temporary recurrent laryngeal nerve paresis and one had persistent hyperparathyroidism.

Conclusion: Although endoscopic parathyroidectomy is technically feasible, its applicability is limited to a minority of patients undergoing operation for hyperparathyroidism. The potential for higher complication and failure rates makes optimism for the procedure appropriately guarded.

Paper accepted 18 July 1999

British Journal of Surgery 1999, 86, 1563–1566

Introduction

Open bilateral parathyroid exploration produces a successful outcome in 95–98 per cent of patients, with minimal complications and a short hospital stay[1,2]. However, in keeping with current trends towards less invasive surgery, there have been a number of recent reports of minimally invasive parathyroidectomy. Various approaches have been attempted including fully endoscopic procedures with gas insufflation, video-assisted procedures via a limited incision, or procedures guided by nuclear mapping or ultrasonographic localization[3–6]. While acceptable short-term results have been achieved, long-term data are not yet available. Of greater concern is the impression that the introduction of minimally invasive parathyroidectomy is, to some extent, a market-driven phenomenon.

In view of these concerns, the Section of Endocrine Surgery of the Royal Australasian College of Surgeons (RACS) recommended that minimally invasive parathyroidectomy should be performed in Australia and New Zealand only within the context of a formal clinical feasibility study reporting to the Australian Safety and Efficacy Register of New Interventional Procedures. The present paper reports the outcome of a feasibility study.

To avoid the potential problems associated with soft tissue insufflation with carbon dioxide, a hybrid technique was used based on limited unilateral exploration through a small suprasternal incision, with location and dissection of the parathyroid adenoma guided by a surgical endoscope, but performed via the incision using standard surgical instruments. This procedure required unequivocal localization of a single parathyroid adenoma with sestamibi scintigraphy. Along with comparison of the outcome and complications, the aim of the study was to assess the feasibility of endoscopic parathyroidectomy and to evaluate its role in the management of hyperparathyroidism.

Patients and methods

This was a prospective, non-randomized and non-blinded study undertaken in a single endocrine surgery unit affiliated to the University of Sydney. Beginning in May 1998, following the recommendation of the Section of Endocrine Surgery (RACS), 100 consecutive patients requiring surgery with a new diagnosis of hyperparathyroidism were evaluated for endoscopic parathyroidectomy. Clinical criteria for mandatory use of the standard open procedure were the presence of coexisting nodular thyroid disease, previous thyroid, parathyroid or cervical surgery, previous cervical irradiation, preoperative evidence of a parathyroid cyst, clinical suspicion of parathyroid hyperplasia or multigland disease, chronic anticoagulation, obesity and physician preference. If none of these criteria was present, a technetium-99m-radiolabelled sestamibi scan was performed to localize a parathyroid adenoma. If sestamibi scintigraphy localized a single parathyroid adenoma unequivocally, the patient was offered the choice of endoscopic parathyroidectomy, after a thorough discussion.

Of the 100 consecutive patients with hyperparathyroidism requiring surgery, 24 patients underwent endoscopic parathyroidectomy. In the remaining 76 patients, 58 were excluded because of coexisting nodular thyroid pathology ($n = 29$), previous surgery ($n = 7$), history of irradiation ($n = 2$), parathyroid cyst ($n = 2$), suspicion of a multiple endocrine neoplasia (MEN) syndrome or familial hyperplasia ($n = 4$), suspicion of a lithium-associated hyperplasia ($n = 3$), secondary or tertiary hyperparathyroidism ($n = 4$), chronic anticoagulation ($n = 3$), obesity ($n = 1$), patient or referring physician preference ($n = 2$), and an incidental parathyroid adenoma found at the time of thyroid surgery ($n = 1$). Forty-two patients were offered a sestamibi scan for localization. Of these, sestamibi scintigraphy failed to localize an adenoma in 13 and suggested possible multiple gland disease in three. Two patients failed to obtain their scheduled scan before operation. Therefore 24 patients met clinical and imaging criteria for endoscopic parathyroidectomy.

There were 22 women and two men in the endoscopic group with a mean(s.e.m.) age of 64(3) years. In the open parathyroidectomy group, there were 60 women and 16 men with a mean(s.e.m.) age of 64(1) years ($P = 0{\cdot}70$).

Surgical techniques

Endoscopically assisted parathyroidectomy was performed under general anaesthesia with the patient in a supine position. A small 25-mm incision was made in a central, suprasternal location. Through the midline, the strap muscles were dissected away from the thyroid capsule on the side ipsilateral to the adenoma. The middle thyroid vein, if present, was ligated and divided under direct vision, and a space was created by blunt finger dissection down to the level of the prevertebral fascia.

A separate stab incision was made posterior to the sternocleidomastoid muscle and a 4·4-mm, 30° surgical telescope was inserted to visualize the previously developed space. Standard surgical instruments were used through the central incision to remove the parathyroid adenoma with visual guidance provided by the endoscope. Endoscopic demonstration of a normal ipsilateral parathyroid gland was then attempted.

Since the aim of the study was to make a comparison with current techniques, open parathyroidectomy was performed in the standard fashion that has been employed in this unit for the past 35 years, namely bilateral exploration and four-gland visualization[7].

Results

Comparing open parathyroidectomy with endoscopically assisted, minimally invasive parathyroidectomy, there were no significant differences in mean adenoma size or operating time. The small difference in postoperative hospital stay was of no real clinical significance (*Table 1*). Outcomes were also similar with respect to resolution of hypercalcaemia. However, the pattern of surgical complications differed.

Of the 76 standard open procedures, eight (11 per cent) involved resection of two enlarged parathyroid glands and seven (9 per cent) were subtotal or total parathyroidectomies for hyperplasia or secondary hyperparathyroidism. The remaining 61 patients (80 per cent) had resection of a single parathyroid adenoma. Excluding subtotal and total parathyroidectomies, 19 right superior, 23 right inferior, 14 left superior and 21 left inferior parathyroid adenomas were removed. There were no glands that had clinical or pathological evidence of parathyroid carcinoma.

By definition, all endoscopic parathyroidectomies resulted in removal of a single gland. Seven adenomas

Table 1 Adenoma size, operating time and postoperative stay

	Endoscopic parathyroidectomy	Open parathyroidectomy	P‡
Adenoma weight (g)*	0·731(0·177)	0·544(0·103)	0·19
Operating time (min)†	74(5)	77(3)	0·43
Postoperative stay (days)	1·9(0·1)	2·3(0·1)	0·04

Values are mean(s.e.m.). *Excludes thyroid tissue removed at open operation; †measurements of operating time included induction and emergence from anaesthesia. ‡Mann–Whitney *U* test were right superior, nine were right inferior, three were left superior and five were in the left inferior position.

Of the 76 patients undergoing open exploration, 39 had a concomitant thyroid procedure (nodulectomy, $n=17$; hemithyroidectomy, $n=11$; bilateral subtotal thyroidectomy, $n=3$; total thyroidectomy, $n=8$). Seventy-three patients (96 per cent) had prompt resolution of the hypercalcaemia and remained normocalcaemic (longest follow-up 12 months). Three patients had persistent hyperparathyroidism. Two patients had unappreciated asymmetrical hyperplasia and one patient had a missed adenoma which was removed successfully at reoperation. Postoperative complications included temporary hypocalcaemia in eight patients (11 per cent). All patients had routine postoperative laryngoscopy; there were no recurrent laryngeal nerve pareses. Two patients had a wound haematoma, one of which required evacuation. There were no wound infections. One patient had a buttock haematoma from prophylactic use of low molecular weight heparin.

Of the 24 patients who had endoscopic parathyroidectomy, 23 had immediate resolution of the hypercalcaemia and remained normocalcaemic (longest follow-up 12 months). The patient with persistent hyperparathyroidism had a single site of uptake on a preoperative sestamibi scan and a single 0·180-g adenoma was removed from the concordant (right inferior) position. Reoperation was undertaken as an open procedure 3 months later; a second parathyroid adenoma (descended right superior) was found in a paraoesophageal position on the same side and two normal left parathyroid glands were identified. Temporary ipsilateral recurrent laryngeal nerve paresis was noted in two patients on postoperative laryngoscopy, which resolved within several weeks of surgery. No patient had postoperative hypocalcaemia, wound infection or haematoma.

Four of the 24 procedures begun endoscopically were converted to standard open parathyroidectomy. One was converted because the adenoma was not visualized; on conversion, a superior parathyroid adenoma was found in a retro-oesophageal location. In two patients, the sestamibi localization was wrong. In one of these, the sestamibi scan indicated an inferior adenoma separate from the thyroid gland, when the adenoma was actually in the standard superior position. In the other, scintigraphy had indicated a left inferior adenoma when, in fact, the patient had a right inferior adenoma. A lesion was indeed present inferior to the thyroid body on the left and was removed with endoscopic assistance; however, frozen-section analysis identified it as a follicular thyroid lesion. The procedure was converted in the last patient because of bleeding from the internal jugular vein encountered after attempted camera placement.

Discussion

This study has demonstrated that endoscopic parathyroidectomy is technically feasible, but before it is embraced it needs to be evaluated critically.

The procedure was not feasible until accurate localization techniques such as high-resolution ultrasonography and sestamibi scintigraphy became available. A limited amount of preclinical experimental work has been published about the development of an endoscopic approach. Brunt *et al.*[8] pioneered this technique in dogs and human cadavers, accessing the pretracheal space via a 2·5-cm central incision, dissecting the perithyroidal space with a balloon and then maintaining it with an external lift retractor. Attempts to use carbon dioxide insufflation resulted in subcutaneous emphysema and pneumomediastinum. Subsequently Norman and Albrink[6,9] confirmed the work in dogs, but observed a number of difficulties in transferring the procedure to patients. Because of limited visualization and blood staining of tissue and camera lens, the endoscopic approach was abandoned in favour of limited exploration guided by intraoperative nuclear mapping[5].

Gagner and co-workers[3,10] also reported endoscopic subtotal parathyroidectomy using carbon dioxide insufflation which was complicated by extensive subcutaneous emphysema. Yeung *et al.*[11–13] described four patients after endoscopic parathyroidectomy and eight after endoscopic thyroidectomy. Recently, a series of 39 patients undergoing endoscopic parathyroidectomy was reported by Miccoli *et al.*[14]. Their technique involved a short carbon dioxide insufflation in combination with external retractors to maintain the operative space. Importantly, the success of the procedure was monitored using intraoperative parathyroid hormone measurement.

Despite these advances, it is clear that it will be difficult to demonstrate clear advantages over the current standard, open, parathyroid exploration. To achieve results equivalent to conventional neck exploration (a high success rate, cost effectiveness, a cosmetically acceptable scar, very low major complication rate and a hospital stay of 1–2 days) careful patient selection will be required. The following criteria could be used to select patients for any minimally invasive parathyroidectomy. First, patients must have an informed discussion with the surgeon about the potential limits of an endoscopic parathyroidectomy and the possibility of conversion to standard neck exploration. Second, a solitary adenoma should be identified unequivocally at a single site using either sestamibi scintigraphy or high-resolution ultrasonography, or both. All patients with apparent multiple gland disease or the likelihood of such pathology (renal failure, family history or suspicion of a MEN syndrome, lithium) should be excluded. Other criteria for exclusion are the presence of coincidental thyroid pathology, a history of previous neck surgery or irradiation, and abnormal skeletal or soft tissue neck anatomy.

The technique of endoscopic parathyroidectomy reported here is an adaptation of the minimal-incision technique and the endoscopic methods of Miccoli, Yeung, Gagner and colleagues. The advantages include the use of standard surgical instrumentation and avoidance of carbon dioxide insufflation. The practical disadvantages are the difficulty in maintaining an appropriate working space, occasional difficulty in visualizing the ipsilateral recurrent laryngeal nerve, leading to an increased risk of nerve paresis, and frequent difficulty in identifying a normal ipsilateral parathyroid gland. In the present experience, this could be accomplished with any degree of certainty in only approximately half the patients.

One disadvantage of all types of directed, minimally invasive parathyroidectomy is the reliance on imperfect localization techniques. In this study localization by sestamibi scanning was incorrect in two of the 24 patients. These concerns were further exposed in a recent retrospective study of patients with primary hyperparathyroidism who had preoperative localization with sestamibi scintigraphy[15]. The scans were correct in only 71 per cent of patients with a single adenoma, 44 per cent of patients with multiple adenomas and none of the patients with hyperplasia. Had the 40 patients undergone unilateral open exploration based on the sestamibi results, a 10 per cent failure rate was predicted. With the difficulties encountered in demonstrating a normal ipsilateral parathyroid gland during endoscopic parathyroidectomy, this failure rate might be expected to increase above that based on the inadequacies of sestamibi scans alone. Although intraoperative parathyroid hormone monitoring was not available for this study, it certainly has the potential to validate any minimally invasive parathyroidectomy technique, to increase the success rate[16] and to avoid the need for visualization of a normal parathyroid gland.

Further studies are clearly required, including a formal assessment of postoperative pain and patient satisfaction, before minimally invasive parathyroidectomy can be judged a cost-effective procedure.

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Complexity- and risk-adjusted model for measuring surgical outcome

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Background: Although currently available surgical scoring systems have good outcome predictive power, their use is often limited by complexity and their non-dynamic nature. The aim of this study was to develop and test a risk adjustment for general surgical audit which is both simple and dynamic, while preserving a high predictive power for surgical morbidity.

Methods: Twelve easily measured, well defined prognostic variables for morbidity were identified from the Otago Surgical Audit data collection form and stratified into suitable categories. Logistic regression was used to adjust for confounding between factors, identifying risk factors with the strongest prognostic value for the outcome of severe and intermediate complications. The resulting model was tested by back-validation and validation.

Results: The derived risk adjustment included all 12 variables. Adjusted odds ratios for all variables were markedly lower than unadjusted values. After logistic regression, the strongest predictors of postoperative morbidity were duration of operation, operation category, inpatient status and organ system in which the procedure was carried out. The area under the receiver operating characteristic curve was 0·86.

Conclusion: A simple dynamic model for surgical morbidity has been developed which is comparable to previously published surgical scoring systems in terms of predictive power. This risk adjustment tool can be incorporated into the existing audit system, enabling comparison of surgical unit performance.

Paper accepted 14 July 1999

British Journal of Surgery 1999, 86, 1567–1572

Introduction

The need to institute a truly patient-centred approach to surgical care has motivated growing interest in measuring the quality of surgical care. Being non-numerical, measuring quality has been quite a challenge. Crude morbidity and mortality rates ('league tables') are limited indicators of the quality of care and are particularly misleading in the comparison of surgical units[1–3], with deleterious consequences for some units[4–6].

Clearly, some method of risk adjustment is needed for the meaningful comparison of performance, both between surgical units and over time. An ideal risk-adjusted scoring system for surgical audit should, in addition to the criteria mentioned by Copeland *et al.*[7], also both involve prognostic variables that are easy to collect[7] and be flexible. Many currently available risk-adjusted scoring systems for surgical audit fulfil these criteria, predicting morbidity and mortality rates to different degrees of sensitivity and specificity[7–9], but they use physiological variables that are more laborious to collect than clinical variables, compromising the completeness of the resultant data set[10].

Existing scoring systems are also relatively static and can reliably be applied only to the data set on which they were developed. As the parameters of such models depend on the data set on which the model was developed, application to data sets with a different case mix may produce significantly misleading outcome predictions[11], challenging the reliability of resulting comparisons between surgical units.

Risk-adjusted scoring systems are developed on existing audit databases. The authors' scoring system was developed on the Otago Surgical Audit for general surgery (developed by the surgery department of the University of Otago) which now holds over 40 000 records and has been implemented in over 100 surgical units worldwide.

This paper describes the development and testing of a dynamic risk- and complexity-adjusted model for general surgical morbidity.

Materials and methods

This scoring system was developed by retrospective analysis of an initial data set of 3643 procedures obtained from the Otago Surgical Audit for general surgery over a 15-month period. The data set comprised all elective and emergency general surgical procedures and included both day cases and inpatients. Six hundred and thirty-eight non-operative cases were excluded from the study. Four duplicate records and five mismatched records, none of which noted complications, were deleted. The remaining 2996 records were available for analysis. Once coding and data entry errors had been corrected by referring to original audit forms, hospital notes and the hospital patient management system, the data set was complete with no missing values.

Twelve prognostic variables were identified from the standard audit form and stratified by clinical judgement. Complication severity was stratified on a scale of 0–3, using the generic descriptions of the complication codes system in the Otago Surgical Audit code book[12]. The data set was divided into two by combining cases with severe or intermediate complications and comparing them against all other cases. Each complication was assigned a severity score and the severity score for the most severe complication was used for analysis.

Both univariate and multivariate logistic regression analyses involving the 12 prognostic variables for morbidity were carried out in SAS (SAS Institute, Cary, North Carolina, USA) version 6.12 for the Power Macintosh (Apple, Cupertino, California, USA). Univariate analysis generated unadjusted odds ratios. Logistic regression determined the association between risk factors and the binary variable for surgical morbidity, taking into account the interaction between risk factors.

This risk-adjusted scoring system was tested by back-validation and validation, as described by Peters and Golding[13]. Back-validation was performed using the data set on which the scoring system was developed. This involved calculation of observed and expected values for variables included in the model (age, operation category, operator and organ system) and variables external to the model (postoperative stay and death). Postoperative stay was divided into two categories: greater than 14 days and 14 days or less. Observed : expected (O : E) ratios were calculated to see if the model was similarly predictive for postoperative stay.

Validation involved testing the risk-adjusted scoring system on another data set from the Otago Surgical Audit for general surgery. The validation data set consisted of 7563 procedures over the subsequent 30-month period. Some 1047 non-operative cases were excluded, leaving 6516 cases for analysis. Duplicate records were deleted, and coding and data entry errors in the validation data set were corrected as outlined for the first data set, leaving a validation data set of 6493 cases with one missing value for sex. Logistic regression excluded the case with the missing value for sex, analysing the remaining 6492 cases.

As there is no established gold standard for determining the predictive ability and goodness of fit of such a model, four different methods were used: the Hosmer–Lemeshow χ^2 statistic[14]; classification tables for 10, 50 and 80 per cent decision criteria[7,11]; receiver operating characteristic (ROC) curves[15,16] and calibration

Table 1 Complication stratification and severity scores

Severity code	Complication type	Definition	No. of cases in development data set (*n* = 2996)
0	No complication	No complication (empty cell) Technical complications (some) e.g. anaesthetic complications Non-operative complications e.g. no lesion found, unexplained fever	2336 (78·0)
1	Minor	Patient discomfort e.g. postoperative atelectasis, urinary retention	358 (11·9)
2	Intermediate	Significant compromise e.g. prolonged ileus; DVT	221 (7·4)
3	Severe	Major threat to life e.g. DIC, MI, renal failure Death	81 (2·7)*

Values in parentheses are percentages. *There were 47 deaths from all causes (1·6 per cent) among the 81 procedures with severe complications; six of the deaths were attributed to advanced cancer. DVT, deep vein thrombosis; DIC, disseminating intravascular coagulation; MI, myocardial infarction curves[11,17]. Detailed descriptions of these methods can be found elsewhere[7,11,14–17].

Results

Tables 1 and *2* show the distribution of complications and the surgical procedures performed. The overall morbidity rate within the development data set was 22·0 per cent; only 7·1 per cent of procedures with complications and 1·6 per cent of the total number of procedures resulted in death. Of the 2996 patients in the development data set, 10·1 per cent (302 admissions) had severe and intermediate postoperative complications.

Table 2 Surgical procedures performed

Procedure	Development data set (n=2996)	Validation data set (n=6492)
Breast and endocrine	204 (6·8)	446 (6·9)
Gastrointestinal	852 (28·4)	1741 (26·8)
Gallbladder, liver, pancreas and spleen	256 (8·5)	401 (6·2)
Gynaecological	15 (0·5)	42 (0·6)
Urological	116 (3·9)	238 (3·7)
Vascular (arterial and venous)	555 (18·5)	1335 (20·6)
Orthopaedic	22 (0·7)	44 (0·7)
Miscellaneous	976 (32·6)	2245 (34·6)

Values in parentheses are percentages

Table 3 Categorization of all 12 prognostic variables

Prognostic variable	Categorization	Development data set prevalence (%)	Univariate odds ratio	Adjusted odds ratio
Age (years)	0–39	37·3	1·0	1·0
	40–69	42·0	2·7 (1·9–3·7)	1·6 (1·1–2·4)
	70–74	7·9	3·8 (2·4–6·0)	1·9 (1·1–3·2)
	⩾75	12·8	6·3 (4·4–9·2)	3·4 (2·2–5·3)
Sex	Male	49·3	1·1 (0·9–1·4)	1·2 (0·9–1·6)
	Female	50·7	1·0	1·0
Timing	Arranged	68·5	1·0	1·0
	Urgent	10·4	3·2 (2·3–4·5)	1·7 (1·1–2·8)
	Emergency	21·1	3·3 (2·5–4·3)	2·4 (1·5–3·9)
Admission	Acute	29·1	2·4 (1·8–3·0)	1·0 (0·6–1·5)
	Not acute	70·9	1·0	1·0
Wound category	Not contaminated or dirty	69·2	1·0	1·0
	Contaminated and dirty	30·8	1·4 (1·1–1·8)	1·0 (0·7–1·4)
Duration of operation (min)	⩽59	64·4	1·0	1·0
	60–119	24·5	4·3 (3·2–5·9)	1·4 (1·0–2·0)
	120–179	7·0	8·4 (5·8–12·3)	1·6 (0·9–2·6)
	⩾180	4·1	15·4 (10·1–23·5)	2·1 (1·2–3·8)
Operation category*	Intermediate and minor	67·8	1·0	1·0
	Major 2	26·2	7·9 (5·8–10·6)	3·4 (2·2–5·2)
	Major 1	6·0	18·1 (12·3–26·6)	5·9 (3·3–10·6)
No. of operations	1	94·3	1·0	1·0
	2	4·2	4·3 (2·9–6·5)	1·9 (1·1–3·2)
	⩾3	1·5	8·1 (4·5–14·7)	4·7 (2·2–10·3)
Operator	Consultant	40·7	3·0 (2·4–3·9)	1·2 (0·9–1·7)
	Registrar	59·3	1·0	1·0
Preoperative stay (days)	> 3	14·2	4·0 (3·1–5·2)	1·4 (1·0–2·9)
	⩽3	85·8	1·0	1·0
Inpatient	Inpatient	82·8	17·5 (6·5–47·1)	2·9 (1·0–8·3)
	Day case	17·2	1·0	1·0
Organ system	Urological	3·9	1·0	1·0
	Gastrointestinal	28·4	17·6 (2·4–127·1)	3·9 (0·5–29·5)
	Gallbladder, liver, pancreas, spleen	8·5	21·3 (2·9–157·0)	3·8 (0·5–29·7)
	Breast and endocrine	6·8	4·1 (0·5–33·7)	1·9 (0·2–16·2)
	Vascular (arterial, venous)	18·6	25·9 (9·4–71·1)	6·8 (0·9–52·2)
	Gynaecological, orthopaedic and miscellaneous	33·8	4·6 (1·7–12·7)	2·8 (0·4–21·6

Values in parentheses are 95 per cent confidence intervals. *Major 2, e.g. cholecystectomy; major 1, e.g. pancreaticoduodenectomy

Comparison of outcome before and after risk adjustment

Table 3 shows the categorization of all 12 prognostic variables included in the model, the proportion of cases which fell into each category, the univariate and adjusted odds ratios and their 95 per cent confidence intervals.

From univariate analysis a few variables stood out as prominent prognostic predictors: duration of operation, operation category, inpatient status and organ system (*Table 3*). Logistic regression adjusts for confounding between variables, generating adjusted odds ratios. Although these variables remained the most influential of the 12 prognostic variables after adjustment, their odds ratios were much reduced. After adjustment for other variables in the development data set, admission category, sex and wound category, all of which had minimal influence on outcome in univariate analysis, were no longer statistically significant.

The model was then tested on a second data set. The adjusted odds ratios were similar to those for the development data set except that for breast and endocrine procedures, which was 0·4 (95 per cent confidence interval (c.i.) 0·1–2·7) compared with 1·9 (0·2–16·2) in the development data set (*Table 3*).

Validation

Overall goodness of fit

The calibration curve in *Fig. 1* shows that the observed and predicted risk of severe and intermediate complications increased in proportion with each other. The diagonal line represents the point at which the O : E ratio is 1·00 for each category of predicted risk. The 95 per cent confidence intervals for the observed morbidity rate at each level of predicted morbidity encompassed this line.

Table 4 is the classification table for the decision threshold of 50 per cent. At one extreme, a 10 per cent decision criteria gave a high sensitivity (79·1 per cent) but also a high false-positive value (71·8 per cent). At the other extreme (80 per cent decision criteria) the low false-positive value (42·9 per cent) was accompanied by a low sensitivity (1·3 per cent).

Fig. 2 shows the receiver operating characteristic curve for the initial data set, the area under the curve being 0·86. The Hosmer–Lemeshow statistic for this model is $\chi^2 = 7{\cdot}0$, 8 d.f. indicating that the model fits the data well.

Table 4 Classification table for decision criteria of 50 per cent

	Observed complications		
	Severe and intermediate	Minimal or none	Total
Expected complications			
Severe and intermediate	45	42	87
Minimal or none	257	2652	2909
Total	302	2694	2996

Sensitivity 14·9 per cent; specificity 98·4 per cent; positive predictive value 51·7 per cent; negative predictive value 91·2 per cent; total correct classification 90·0 per cent

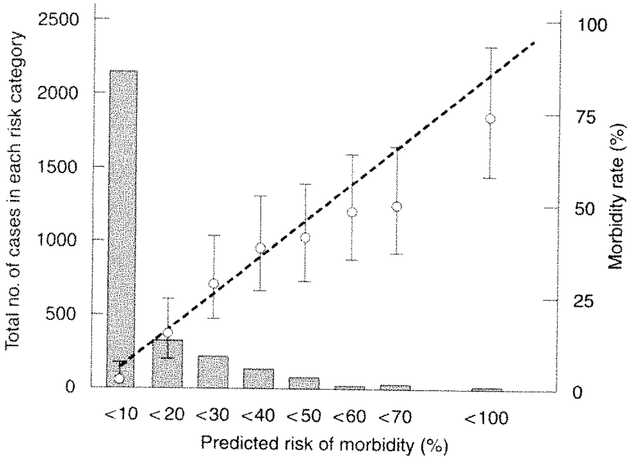

Fig. 1 Calibration curve for surgical morbidity (symbols with 95 per cent confidence intervals) showing no significant deviation from the diagonal line, which represents an observed : expected ratio of 1·00

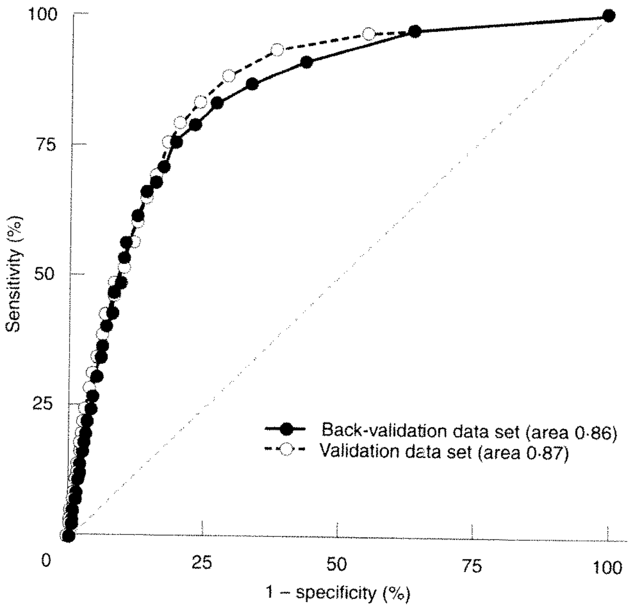

Fig. 2 Receiver operating characteristic curves for morbidity

Uniformity of fit

On internal validation by age, operator, operation category and organ system, none of the O : E ratios departed significantly from 1·00, with all 95 per cent confidence intervals encompassing 1·00. The model was also externally validated by postoperative stay, the O : E ratios for which differed significantly from 1·00 (O : E 0·72–1·61; 95 per cent c.i. 0·61–1·89). External back-validation of the model by death yielded a similarly poor fit. For the validation data set, internal validation O : E ratios did not differ significantly from 1·00 (O : E ratio 1·00; 95 per cent c.i. 0·12–2·92) and those for external validation were of similar poor fit to the development data set.

Discussion

Any risk-adjusted scoring system is dependent on complete and accurate recording of information in the parent audit[10]. The development data set from the Otago Surgical Audit for general surgery had no missing values. If missing values are present in other data sets on which this risk-adjusted scoring system is to be tested they could be replaced using methods such as the Speigelhalter–Knill-Jones method[18].

Logistic regression decreased the magnitude of the univariate odds ratios for most variables, indicating some degree of confounding among the variables and highlighting the need for risk adjustment, without which crude morbidity estimates would overemphasize the relative importance of prognostic variables and provide misleading estimates of outcome[1–3].

Despite the need for further investigation to explain the difference between the adjusted odds ratios of the two data sets for breast and endocrine procedures fully, the presence of such a difference indicates the need for a dynamic risk adjustment model. The wide 95 per cent confidence intervals for the adjusted odds ratios for organ system reflect the small sample size of the reference category.

Although three of the 12 variables had no prognostic role after logistic regression, they were not excluded because this model is dynamic. In such a model, variables that may be of little prognostic significance when the model is applied to this particular data set may be more important when the model is applied to another data set.

All four methods of measuring overall fit indicate that the model fits both development and test data sets well. These results are comparable to other currently available scoring systems for surgical audit such as the Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (area under the receiver operating characteristic curve 0·84)[9]. More in-depth comparison of any two such systems requires simultaneous prospective analysis of the two systems on the same data set.

The optimal operating point on the receiver operating characteristic curve, defined elsewhere[16], should ideally be determined by cost–benefit analysis[16]. By the simpler method outlined by Metz[16], the operating point for this study is at a decision threshold of 12 per cent, sensitivity 76·5 per cent and specificity 80·8 per cent.

Testing the uniformity of fit is an important validation tool for any risk adjustment; a model that may seem to provide good overall fit may be of poor fit for certain subsets of the data set.

Initially, the model significantly overpredicted morbidity for vascular surgery (O : E 1·29; 95 per cent c. i. 1·06–1·57). Inclusion of organ system as a prognostic variable provided the model with the uniformity of fit required in order to be applied with potential reliability to surgical specialty subsets of a given data set.

The model further shows good fit for subcategories of predicted risk (O : E 0·71–1·18), the wide 95 per cent confidence intervals at higher levels of predicted risk reflecting the small number of observations in these subcategories.

Poor fit of the model on external back-validation against postoperative stay and death indicates that, although the model can be used to predict the risk of postoperative morbidity, it cannot be applied as a general model to predict other surgical outcomes without further outcome-specific risk adjustment.

The simplicity of this model is twofold: variables are easily collected and the outcome of the risk adjustment is presented in the easily interpretable form of O : E ratios, rather than being a relatively arbitrary score. This scoring system uses clinical and operative variables rather than physiological variables, reducing the likelihood of missing values, and the cost and resource wastage involved in determining physiological variables. The clinical variables used in this model have the advantage of being low-cost parameters that are almost universally recorded routinely for every operative procedure. These advantages make this scoring system easier for surgeons to apply retrospectively for the assessment of surgical performance.

To eliminate the question of whether poor fit is a direct consequence of model inflexibility, the weights for prognostic variables need to vary with each data set to which the model is applied. With such a flexible model, any outlier values can potentially be clearly identified as being genuine outliers that require further investigation, rather than a misleading consequence of an inappropriate model.

This study has shown that a risk adjustment model based purely on clinical rather than physiological parameters can have comparably high-outcome predictive power. The model described here is a flexible, uniformly fitting and simple risk adjustment for predicting surgical morbidity.

Risk adjustment tools such as this one are ultimately developed to be used for the comparison of surgical unit performance. In the comparison of surgical units, significant variances in outcome which warrant detailed examination are defined as those with O : E ratios that lie outside the 95 per cent confidence limits for the data set. This scoring system also potentially enables the evaluation of surgical practices with both a diversity of procedures and relatively small numbers in the subgroups.

Acknowledgements

The authors thank Mr T. Elliott, Mr R. A. Pettigrew and Dr J. Kennedy for their input and helpful comments at various stages of this study.

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Fatal and life-threatening complications in antireflux surgery: analysis of 5502 operations

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Background: There have been few comprehensive studies relating to the life-threatening or fatal complications of antireflux surgery.

Methods: Some 5502 antireflux operations were performed in Finland between January 1987 and January 1996 (population approximately 5 million); 3993 procedures (72·6 per cent) were open fundoplications, 1162 (21·1 per cent) laparoscopic fundoplications and 347 (6·3 per cent) other antireflux procedures.

Results: There were 43 fatal or life-threatening complications (prevalence 0·8 per cent). Twenty-two followed primary open fundoplication (prevalence 0·6 per cent), 15 laparoscopic fundoplication (prevalence 1·3 per cent) ($P < 0·05$), one refundoplication and five other antireflux procedures. The overall mortality rate was 0·3 per cent. Nine patients (0·2 per cent) died after open fundoplication, one (0·1 per cent) following laparoscopic fundoplication ($P = 0·43$), one following refundoplication and four after other antireflux procedures. Laparoscopic fundoplication was followed by 14 non-fatal life-threatening complications (prevalence 1·2 per cent), open fundoplication by 13 (prevalence 0·3 per cent) ($P < 0·01$) and other antireflux procedures by one life-threatening complication (0·3 per cent).

Conclusion: Laparoscopic fundoplication was associated with more life-threatening complications than open fundoplication. This may compromise the advantages of the laparoscopic technique.

Paper accepted 22 July 1999

British Journal of Surgery 1999, 86, 1573–1577

Introduction

Using correct techniques and appropriate indications the success rate after antireflux surgery is usually 80–90 per cent[1,2]. The most common antireflux procedures are total (Nissen) or partial (Toupet, Belsey, etc.) fundoplication. Fundoplication can be performed via laparotomy[3], thoracotomy[4], laparoscopy[5] or by thoracoscopy[6]. Hill's gastropexy, oesophageal lengthening procedures (Collis–Nissen, Collis–Belsey) and partial gastrectomy with Roux-en-Y reconstruction[7] are less usual, and are employed in complicated cases.

The minor drawbacks of antireflux surgery are postoperative symptoms including dysphagia (prevalence 3–43 per cent), bloating (0–50 per cent) and increased flatus (30–47 per cent)[8–11]. Unfortunately, there are also major complications, some of which can be life threatening or fatal. The reported frequency of serious complications after antireflux surgery has varied, ranging from 0·7 to 4·5 per cent[12,13]. The large statistical variation may be caused by several factors, the most significant of which include the lack of adequate postoperative follow-up and the small numbers of antireflux operations performed in an individual institution.

Since the introduction of laparoscopic antireflux surgery, the number of antireflux operations in Finland has been increasing[14]. Similar trends have been reported elsewhere[15]. Very few comprehensive studies relating to serious complications after antireflux procedures have been made, especially those involving the laparoscopic technique. As a result, this study was performed to analyse serious complications after antireflux surgery, including both open and laparoscopic fundoplications, in 5502 patients.

Patients and methods

All hospitals in Finland licensed to perform surgical interventions must report all surgical procedures performed every year to the National Research and Development Centre for Welfare and Health. Each operation has a separate code number so all the antireflux procedures performed are reliably detected from this system.

The number of antireflux procedures performed in Finland (population approximately 5 million) during the 10-year period from 1 January 1987 to 1 January 1996 was obtained from the National Research and Development Centre for Welfare and Health. The Patient Insurance Association was founded in 1987. Patient insurance is obligatory in Finland, and it is not possible to practise medicine without having it. In this system the patients themselves make notifications concerning patient injuries, and every notification has to be dealt with. The reliability concerning major complications is generally regarded as all inclusive.

The death certificates of all patients who had died because of an antireflux operation were obtained from the Finnish Central Statistical Office, and the hospital records relating to these patients were examined. In addition, all notifications of patient injury following antireflux surgery for the same period were obtained from the Patient Insurance Association and analysed. The medical records of all patients who had experienced these fatal and near-fatal complications were retrieved. However, only life-threatening complications were taken into account, including oesophageal or gastric perforations leading to mediastinitis or peritonitis. In addition, massive intraoperative bleeding and septic intra-abdominal abscesses resulting in repeated reoperation and lengthy hospitalization (more than 30 days), and total oesophageal obstruction unresponsive to dilatation and leading to permanent parenteral nutrition were classified as life-threatening complications. Wound infections and potentially severe postoperative complications which were not life threatening and did not necessitate a hospital stay of more than 30 days (i.e. splenic injuries, oesophageal or gastric perforations and haemorrhage) were excluded.

The Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, and the Ministry of Health and Welfare of Finland approved this study.

Statistical analysis

The χ^2 two-tailed and Fisher two-tailed exact tests were used to assess the statistical significance of differences. $P < 0.05$ was taken as indicating significance.

Results

According to the National Research and Development Centre for Welfare and Health 5502 antireflux procedures were performed in Finland (population approximately 5 million) during the 10 years from 1 January 1987 to 1 January 1996. Total or partial fundoplication was used in 5155 patients (93·6 per cent). Some 3993 fundoplications (77·5 per cent) were performed using an open technique and 1162 (22·5 per cent) using a laparoscopic technique.

Antireflux operation was stated as the cause of death on 15 death certificates. Moreover, there were 111 notifications of patient injury, caused by the complications of antireflux surgery, to the Patient Insurance Association. Using the above-mentioned criteria 28 (25·2 per cent) were classified as life threatening. Accordingly, there had been 43 life-threatening complications (prevalence 0·8 per cent) of which 15 proved fatal (prevalence 0·3 per cent).

Life-threatening complications after open fundoplication

Twenty-two life-threatening complications (in 15 men and seven women, of mean age 57 (range 19–77) years) followed primary open fundoplication. Laparotomy had previously been undertaken in seven of these patients. Three of them had undergone previous hiatal dissection (two of whom had gastric perforation). Operative risk factors existed in 18 of the patients with complications.

There were nine fatal and 13 life-threatening complications after primary open fundoplication (*Table 1*). The mortality rate was 0·2 per cent and the prevalence of life-threatening complications was 0·3 per cent. Due to serious complications shown in *Table 1*, the final causes of death were intra-abdominal infection in five patients, mediastinitis in two, intra-abdominal haemorrhage in one and pneumonia in one patient.

Twenty patients underwent from one to six (mean two) additional operations (*Table 2*), and two patients (one with oesophageal perforation, one with mediastinitis) were managed conservatively. All gastric perforations occurred in the fundic area.

Complications were diagnosed 0–34 (mean 7) days after operation. Three oesophageal perforations were diagnosed at operation. In the 19 remaining patients who were not diagnosed intraoperatively, complications were diagnosed in eight at exploratory laparotomy performed for peritonitis, septic fever, respiratory distress or hypotension and in 12 because of pathological radiographic studies. In the 19 patients mentioned above the diagnostic delay ranged from 0 to 32 (mean 2) days.

Life-threatening complications after laparoscopic fundoplication

Fifteen life-threatening complications (in eight men and seven women of mean age 52 (range 31–76) years) were caused by primary laparoscopic fundoplication. There had

Table 1 Life-threatening and fatal complications in antireflux surgery

	Open fundoplication (*n*=22)	Laparoscopic fundoplication (*n*=15)	Other antireflux procedure (*n*=6)
Oesophageal perforation	7 (2)	4	2 (1)
Gastric perforation	8 (4)*	6 (1)	1 (1)†
Intra-abdominal abscess	3 (1)	0	0
Oesophageal obstruction	0	3	0
Intestinal complications*	3 (2)	0	1 (1)
Intra-abdominal haemorrhage	0	2	0
Mediastinitis	1	0	0
Pneumonia	0	0	1 (1)
Heart failure	0	0	1 (1)

Values in parentheses are fatal complications. *Including one mesenteric arterial thrombosis and three intestinal perforations; †death after reoperation for failed antireflux operation

Table 2 Reoperations because of fatal and life-threatening complications after open and laparoscopic fundoplication

	Open (*n*=20)	Laparoscopic (*n*=14)
Closure of perforation	14	5
Abscess canalization or reoperation for operative bleeding	8	6
Refundoplication	3	4
Wrap takedown	3	3
Reduction of stomach from chest (one subtotal gastrectomy)	3	1
Intestinal resection	2	1
Oesophageal resection	3	6
Lower lobectomy of left lung	1	0
Thoracoplasty	1	0
Other	3*	1†

*Including one transverse colostomy, one regastrostomy and one hernia repair; †one laparoscopy and cutting of the uppermost suture

been no previous laparotomies in this group. A risk factor existed in six of the 15 patients with complications.

There was one fatality (due to intra-abdominal sepsis) and 14 non-fatal life-threatening complications (*Table 1*). Accordingly, the mortality rate after laparoscopic fundoplication was 0·1 per cent. There was no significant difference in mortality rate between the open and laparoscopic fundoplication groups ($P = 0{\cdot}43$). However, the prevalence of life-threatening complications was 1·2 per cent, significantly greater than that in the open fundoplication group ($P < 0{\cdot}01$). A fatal or a non-fatal life-threatening complication occurred in 15 patients, a greater prevalence than that after the open technique ($P < 0{\cdot}05$).

Reoperations (one to eight (mean two) per patient) were necessary in 14 patients (*Table 2*), and one patient with gastric perforation was treated conservatively. The latter patient was the only one who died in this group. All gastric perforations occurred in the fundic area. The major mechanism of gastric perforation was instrument handling (three cases).

Complications were diagnosed 0–9 (mean 2) days after operation. Four oesophageal perforations were diagnosed during operation. Of these, two had laparoscopic and two had open repair. Complications were diagnosed in five of the other 11 patients, who were not diagnosed intraoperatively, at laparotomy performed for signs of peritonitis, septic fever, respiratory distress or hypotension , and the remaining six were diagnosed by pathological radiographic studies. The diagnostic delay in the 11 patients mentioned above ranged from 0 to 14 (mean 1) days.

Life-threatening and fatal complications after reoperation for failed antireflux operations and antireflux procedures other than fundoplication

Three life-threatening complications followed partial gastrectomy with Roux-en-Y reconstruction, two arose after other antireflux operations (one Husfeld's plasty, one hiatal repair with gastropexy) and one after reoperation for a failed antireflux operation. The mean age of the three men and three women in this group was 63 (range 36–83) years. Three patients had ischaemic heart disease. One patient had previously undergone a laparotomy.

Three of the six procedures used in this group were partial gastrectomies with Roux-en-Y reconstruction. One was a Husfeld's plasty, one was a gastropexy with hiatal repair and one was refundoplication. Owing to one oesophageal stricture and two concomitant peptic ulcers all partial gastrectomies (including vagotomy) were primary operations. Three additional procedures were performed: two cholecystectomies and one oesophageal dilation.

There were five fatal and one life-threatening complication. Causes of death were intra-abdominal infection in three cases, pneumonia in one and heart failure in one. Life-threatening complications and associated complications in fatal cases are shown in *Table 1*.

The number of reoperations per patient varied from one to two (mean two per patient) in four patients. The diagnostic delay ranged from 0 to 22 (mean 5) days. Complications were diagnosed by laparotomy in three after signs of peritonitis, in two by pathological radiographic study and in one at autopsy.

Discussion

In recent years, the reported mortality rate after open fundoplication has ranged from 0 to 1·3 per cent[16,17]; that after the use of laparoscopic techniques has ranged from 0 to 1·4 per cent[18–20]. In this study, the annual mortality rate of antireflux surgery in Finland ranged from 0 to 0·5 per cent (mean 0·3 per cent). There were no statistically significant differences in mortality rate between the open and laparoscopic fundoplication groups. After open fundoplication, the mortality rate was 0·2 per cent compared with 0·1 per cent after use of the laparoscopic technique. The overall mortality rate after 5502 antireflux operations was 0·3 per cent (15 patients); these figures are very similar to those reported in earlier studies[16–20]. Because there is no clear definition of life threat, the numbers of serious complications in this study cannot be compared directly with the numbers reported in earlier studies. However, the reported incidence of major complications has ranged from 0·7 to 4·5 per cent of patients[12,13].

After antireflux procedures other than fundoplication the mortality rate in this study was 1·2 per cent. Three of the four fatalities in this group occurred after partial gastrectomy and Roux-en-Y reconstruction. Hence, it is evident that Roux-en-Y partial gastrectomy should be reserved for complicated cases.

The mortality rate after failed antireflux surgery has generally ranged from 0 to 5 per cent[21–25], although a mortality rate as high as 17·6 per cent has also been reported[26]. Only one death after reoperation was evident in the present study. In this group the mortality rate cannot be calculated because there is no distinct hospital discharge code for subsequent operations following failed antireflux surgery.

In this study the annual prevalence of serious (fatal or life-threatening) complications after antireflux surgery ranged from 0 to 1·4 (mean 0·8) per cent. Serious complications were most frequent in 1993 (in absolute or percentage terms). In that year the number of antireflux operations performed in Finland had also reached a maximum[14]. The introduction of laparoscopic techniques in 1992 was probably the most significant cause of the increase in both the number of antireflux operations and further complications.

Laparoscopic fundoplication has been responsible for a significantly greater number of life-threatening complications than the open procedure. The newness of the technique may have been the most significant cause; surgeons were not yet fully acquainted with all the aspects of its utilization. Moreover, patient selection may have been problematic as well; not all patients are suited to a laparoscopic approach and the technique was not as yet properly adapted[27].

There were considerable delays in diagnosing the complications of antireflux surgery. The mean diagnostic delay was 2 days after open fundoplication, 1 day after laparoscopic fundoplication and 5 days after other antireflux procedures. The mean delay between the beginning of alarming symptoms and intervention was even greater: 5 days after open surgery, 6 days after laparoscopic fundoplication and 5 days after other antireflux procedures. Severe abdominal pain, septic fever, respiratory difficulties or hypotension, alone or in combination, were seen in every patient. Abdominal pain, hypotension and septic fever were most often the primary symptoms; respiratory difficulties followed. If oesophageal or fundic perforation is suspected, a water-soluble contrast swallow, with the patient in a supine position, should be obtained without delay[28].

In the present study, as in others[1,9,12,13,17,29], the most frequent and serious complication in both the open (16 of 23 procedures, including one refundoplication) and laparoscopic (ten of 15) groups was perforation of the oesophagus or fundus. However, there were also specific serious complications related to both fundoplication techniques including intra-abdominal abscesses and intestinal problems (six of 23) in the open group, and total oesophageal obstruction and intra-abdominal haemorrhage (five of 15) in the laparoscopic group.

In conclusion, more life-threatening complications were perceived after laparoscopic than after open fundoplication. These findings may indicate that there are actually fewer advantages to laparoscopic techniques than may initially be apparent. This must be considered both in planning operation and informing patients.

Acknowledgements

The authors thank Mrs Yvonne Sundström for skilful assistance in this study.

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Original article

Value of a surgical high-dependency unit

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Background: A minority of hospitals in the UK have a high-dependency unit (HDU). One reason for this is a lack of evidence supporting its benefit. This study sought to compare the outcomes of patients undergoing major abdominal surgery with regard to HDU utilization.

Methods: Data were collected prospectively from two groups of patients over 10 months. Patients in the no-HDU group underwent major abdominal surgery in a hospital without an HDU and returned to a general surgical ward. The other group was managed initially in an HDU. Data collected included Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) scores, complications, deaths and length of stay.

Results: Physiological and operative scores as calculated on the RAJIS POSSUM software were similar in both groups. The HDU group comprised 121 patients. Sixty-four developed a complication whereas 58·81 were expected to, giving an observed : expected (O : E) ratio of 1·09. Sixteen deaths occurred and 14·54 were expected (O : E ratio 1·10). Some 50 per cent stayed in hospital longer than was predicted. The no-HDU group comprised 71 patients. Fifty-nine developed a complication compared with 33·82 expected (O : E ratio 1·74). Ten deaths occurred, whereas 8·88 were expected, giving an O : E ratio of 1·13. Some 63 per cent stayed longer than predicted. The O : E ratios for morbidity were significantly different ($P < 0.0005$). The complications that occurred more frequently in the absence of an HDU were chest infection, arrhythmias and hypotension.

Conclusion: Postoperative management on an HDU was associated with fewer cardiorespiratory complications. There was no difference in mortality rate but there was a trend towards shorter hospital stay.

Paper accepted 1 September 1999

British Journal of Surgery 1999, **86**, 1578–1582

Introduction

Only a minority of hospitals in the UK have a high-dependency unit (HDU). Reasons for this include the cost of setting up a unit, disagreement over who should be responsible for running the unit and a lack of evidence supporting the benefit of such a facility. The purpose of an HDU is to provide patients with a level of nursing and medical care somewhere between that provided by an intensive care unit (ICU) and that which is available on a general ward. The principle advantages are in providing adequate analgesia and oxygenation, and good fluid balance[1].

In hospitals without an HDU, about one-third of the beds in the ICU are occupied inappropriately by high-dependency patients[2–5]. This results in fewer ICU beds being available for the critically ill, and is an inefficient use of this scarce resource. Alternatively, patients needing HDU care may be managed on the general ward where they may not receive optimal care and so will be at risk of an adverse outcome[6].

A prime motivating factor in the development of HDUs for surgical patients has been the report of the National Confidential Enquiry into Perioperative Deaths[7], which pointed to a need to provide improved postoperative care. Modern management of the patient after operation involves the use of specialized equipment and techniques. The concentration of all patients in the hospital into a single unit allows the staff to become highly experienced in the techniques of critical care. It also encourages medical staff to have an efficient review process.

Many factors influence postoperative recovery including patient attitude, co-morbidity, surgical expertise and the postoperative environment. The postoperative care of general surgical patients in two district general hospitals serving similar communities was therefore studied to investigate the effects of provision of an HDU. Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) scoring was used to standardize the patient groups. The critical events included morbidity, death and length of stay in hospital. Only one of the two hospitals had an HDU.

Patients and methods

Data were collected prospectively from consecutive patients undergoing major abdominal surgery in two hospitals staffed by two different sets of surgeons. Patients in the no-HDU group underwent surgery over 10 months in a hospital without an HDU and returned to a general ward after operation. The second group was managed on an HDU following the operation, and data were collected over 5 months. No patient who went to an ICU immediately after operation was included. Similar antibiotic prophylaxis policies were used in both hospitals.

The HDU is a six-bed unit that provides a 1 : 2 nurse to patient ratio. A basic surgical trainee is based on the unit from 09.00 to 17.00 hours and provides on-call cover at other times. Patients are closely monitored and can be supported up to the point of requiring ventilation or dialysis. Nurses are specifically trained in HDU and some ICU techniques. Physiotherapy staff are allocated to the unit.

The general surgical ward provides a 1 : 6 nurse to patient ratio. The immediately available doctor is a preregistration houseman.

Data collected included the POSSUM score[8], which is derived from 12 physiological variables measured before operation and six factors related to the operative procedure. Data were collected manually in each hospital and then entered on to a database at the hospital with an HDU where it was analysed using the commercially available software RAJIS (Hyperhelp, Cheshire, UK). Data on complications as defined in the POSSUM system, deaths and length of stay were collected. The POSSUM scores were used to obtain the predicted risks of morbidity and death for each patient and thence the expected morbidity and mortality rates for each group. The observed incidence of complications and death could then be compared with the expected values, to give an observed to expected (O : E) ratio. The POSSUM system also gives a predicted length of stay based on the physiological and operative scores.

Statistical analysis was performed using the χ^2 test and regression analysis.

Results

The HDU group comprised 121 patients, 48 women and 73 men, with a median age of 70 (range 16–95) years. There were 71 patients in the no-HDU group, 38 women and 33 men, with a median age of 70 (26–94) years. POSSUM scoring revealed a median physiological score of 21 (range 12–50) for the HDU group and 19 (12–36) for the no-HDU group, indicating slightly less disturbance in the physiological parameters in the latter group, although this was not significant. Median operative scores were 15 (9–29) for the HDU group and 16 (10–36) for the no-HDU group. The operations performed are listed in *Table 1*.

Table 1 Operations

Operation	HDU	No HDU
Colorectal		
Appendicectomy (laparotomy)	2	2
Right hemicolectomy	12	8
Transverse colectomy	1	1
Left hemicolectomy	2	5
Sigmoid colectomy	6	8
Hartmann's procedure	6	3
Anterior resection	10	5
Abdominoperineal resection	5	5
Subtotal colectomy	4	2
Iliocolic bypass	2	
Defunctioning colostomy	4	
Reversal of Hartmann's	2	
Repair of perforated colon	1	
Colotomy	2	
Upper gastrointestinal/hepatobiliary		
Oesophagogastrectomy	4	
Total gastrectomy	2	1
Partial gastrectomy	3	14
Repair of ulcer	4	5
Resection of ileum	5	4
Formation of jejunostomy	2	
Enterotomy	2	
Other upper gastrointestinal procedures	6	
Cholecystectomy	9	2
Bile duct procedure	2	
Drainage of pancreatic cyst	2	
Splenectomy	2	
Repair of liver laceration	1	
Other		
Division of adhesions	8	2
Drainage of peritoneal cavity	1	2
Opening of peritoneal cavity	9	2

HDU, high-dependency unit

Morbidity

In the HDU group the median predicted risk of morbidity was 59 (range 11–99) per cent and in the no-HDU group it was 57 (range 15–99) per cent. Among the HDU group 64 patients developed a clinically significant complication, compared with an expected 58·81, giving an O : E ratio of 1·09. In the no-HDU group, 59 patients developed a complication, whereas the expected number was 33·82, giving an O : E ratio of 1·74. The difference in O : E ratios between the two units was highly significant ($P < 0\cdot0005$, χ^2 test).

The complications that occurred are shown in *Table 2*. There was a statistically significant increase in cardiac and respiratory complications in the no-HDU group. The critical events resulting in the complications are shown. Chest infection, dysrhythmia and prolonged hypotension were more common in the no-HDU group; an increased incidence of wound infections was also seen in this group.

Table 2 Complications and critical events

	HDU	No HDU	P*
Respiratory	43 (36)	36 (51)	0·0392
Chest infection	30 (25)	29 (41)	0·02
Respiratory failure	6 (5)	4 (6)	
Pleural effusion	5 (4)	3 (4)	
Pulmonary collapse	1 (1)	0	
Other	1 (1)	0	
Cardiac	14 (12)	24 (34)	0·0002
Myocardial infarction	1 (1)	2 (3)	
Cardiac failure	3 (2)	3 (4)	
Dysrhythmia	9 (7)	9 (13)	
Hypotension	1 (1)	10 (14)	0·0002
Renal failure	2 (2)	2 (3)	
Infection			
Wound	3 (2)	12 (17)	0·0003
Septicaemia	5 (4)	2 (3)	
Other	2 (2)	7 (10)	
Haemorrhage	3 (2)	3 (4)	
Thrombosis			
Deep vein thrombosis	2 (2)	0	
Pulmonary embolism	2 (2)	2 (3)	
Other	1 (1)	1 (1)	
Wound dehiscence	3 (2)	1 (1)	
Anastomotic leak			
Minor	1 (1)	1 (1)	
Major	0	2 (3)	

Values in parentheses are percentages. HDU, high-dependency unit. *χ^2 test

Deaths

The median predicted risk of death was 14 (range 2–97) per cent) in the HDU group and 13 (range 3–92) per cent in the no-HDU group. In the HDU group there were 16 deaths, compared with 14·54 expected, giving an O : E ratio of 1·10. In the no-HDU group ten deaths occurred, whereas 8·88 were expected, resulting in an O : E ratio of 1·13. This difference was not statistically significant.

Length of stay

For patients in the HDU group the median length of stay in hospital following the operation was 10 (range 2–60) days. The median predicted stay was 11 (range 3–233) days. Sixty-one patients (50 per cent) stayed longer than expected, by a median of 3 (range 1–46) days, and 60 patients (50 per cent) stayed for a shorter time than was predicted, by a median of 7 (range 1–203) days.

For those in the no-HDU group the median duration of postoperative stay was 14 (range 0–55) days compared with a predicted stay of 11 (range 4–161) days. Forty-five patients (63 per cent) overstayed their prediction, by a median of 7 (range 1–35) days and 26 patients (37 per cent) had a shorter than predicted stay, by a median of 11 (range 1–161) days. This difference was not significant.

Analysis by surgical specialty

A total of 98 patients underwent a colorectal procedure, 59 in the HDU group and 39 in the no-HDU group. The O : E ratios for morbidity were 0·97 in the HDU group and 1·87 in the no-HDU group (P not significant). The O : E ratios for death were 0·97 in the HDU group and 1·05 in the no-HDU group (P not significant). However, the four patients who died in the no-HDU group all had a predicted mortality risk of less than 40 per cent, whereas in the HDU group all four had a predicted risk of greater than 48 per cent.

Seventy patients underwent an upper gastrointestinal or hepatobiliary procedure, 44 in the HDU group and 26 in the no-HDU group. In both groups the observed morbidity exceeded the predicted value. The O : E ratio was 1·93 in the HDU and 2·40 in the no-HDU group. A majority of patients in each group experienced a respiratory complication, most commonly a chest infection. The mortality O : E ratios were 1·02 (HDU) and 1·89 (no-HDU). Again the morbidity ratios were statistically different, whereas the mortality ratios were not.

Twenty-four patients underwent a miscellaneous laparotomy, 18 in the HDU group and six in the no-HDU group. The O : E ratio for morbidity was 1·16 in the HDU group and 1·58 in those managed without an HDU. For deaths the ratios were 1·19 for the HDU and 0·57 for the no-HDU groups.

Discussion

The aim of this study was to establish the clinical benefits of postoperative care in an HDU compared with a standard general surgical ward. The ideal comparative study would have been performed within one hospital. However, the nurses and surgeons in the hospital did not consider it an ethical option to randomize patients to receive high-dependency care or not when such a unit has been available for many years.

Factors other than postoperative care influence patient outcome but the use of the POSSUM system enables comparison of the physiological and operative scores of patients undergoing similar operations in each unit. The two groups of patients were standardized for severity of illness and magnitude of operation. O:E ratios were compared between the units rather than crude morbidity and mortality rates. The excess complications in the group managed without an HDU were not of a technical nature which probably reflected a similar quality of surgical expertise between the two hospitals. The complications were primarily cardiorespiratory, exactly the type of complication that could be avoided by closer attention to fluid balance, oxygenation and analgesia.

There was a significant improvement in outcome for the patients who were managed initially in the HDU rather than a general ward, as reflected by the incidence of complications. The specific complications that occurred less commonly in the HDU group were chest infections (25 *versus* 41 per cent), prolonged hypotension (1 *versus* 14 per cent), dysrhythmia (7 *versus* 13 per cent, although this was not significant) and wound infection (2 *versus* 17 per cent). The reduced incidence of cardiovascular and respiratory complications may be explained by a close attention to pain control and fluid balance in the HDU. The significantly reduced incidence of hypotensive episodes in the HDU probably reflects the vigilance of the nurses and the presence on the HDU of a doctor who is able to respond promptly.

The alleviation of pain is important in minimizing the perioperative stress response[9], enhancing respiratory function and so reducing the incidence of respiratory complications. Modern techniques to relieve postoperative pain require specialized supervision and technical knowledge[10–12]. The use of intravenous opiate infusions or epidural narcotics is beneficial but can be dangerous if a patient is not monitored carefully. The HDU environment has allowed the development of safe and effective epidural and intravenous analgesia. The majority of patients in both groups in this study received epidural analgesia after operation.

Many of the patients who benefit from high-dependency care following surgery, such as the elderly and those undergoing emergency surgery, are prone to develop both renal and cardiac impairment[13]. Closer observation of fluid balance allows earlier intervention and should therefore reduce the incidence of protracted hypotension, cardiac overload and acute renal failure. There is some evidence that on a general ward the nurses instinctively look after the most ill patient, possibly to the detriment of patients with less serious conditions[14]. This is particularly the case at night when a reduced service is provided.

There was no significant difference in mortality rate between the two groups, although as the number of deaths in each group was small this was not surprising. However, particularly in the colorectal subgroup, there was a tendency for the deaths in the no-HDU group to occur in patients banded at lower risk. There was a trend towards shorter postoperative stay in hospital in all the subgroups that went to an HDU although this did not reach statistical significance.

The placement of high-dependency patients in an ICU can create a number of problems. In most hospitals the ICU beds are constantly under pressure. It was not the practice of the hospital with no HDU in this study to place any patient in the ICU who did not require intensive care. However, a number of studies of ICUs in hospitals without HDUs have found that between 21 and 40 per cent of the ICU beds are occupied inappropriately by high-dependency patients[2–5,15]. Housing high-dependency patients in scarce ICU beds may necessitate transfer of patients to other hospitals or nursing critically ill patients elsewhere, such as the recovery room. Patients already in the ICU may be discharged prematurely[16]. Another problem is that major elective surgery requiring an intensive care bed may be postponed[2,17]. The provision of an HDU alleviates these problems. It also enables earlier discharge from the ICU in some patients who may benefit from step-down care rather than going straight back to a general ward.

In spite of these factors, few hospitals in the UK provide this facility. In 1995, 15 per cent of hospitals in the UK had an HDU[18], and Coggins and de Cossart[12] reported that the number had fallen from 55 hospitals in 1988 to 33 in 1995. Nehra *et al.*[19], however, found that between 1981 and 1991 the number of patients requiring high-dependency care had almost doubled and that these patients were needing such care for longer.

The establishment of an HDU requires considerable expenditure, although cost saving will occur once the unit is running. However, moving high-dependency patients out of the ICU will not necessarily save money as the demand for ICU, as well as HDU, beds continues to rise and will expand to fill the available facilities[1].

Another argument against an HDU is that concentrating ill patients in one area will deprive staff on the general wards of the skills and satisfaction acquired through the care of critical patients. To equip a specific number of ward-based beds and train surgical ward nurses up to the level attained in an HDU could be an alternative, but with ever-increasing technology it may be unreasonable to expect staff not regularly using these sophisticated techniques to maintain the necessary level of expertise.

This study has demonstrated significant clinical advantages of monitoring patients in an HDU after operation, particularly with respect to the development of cardiorespiratory complications. A larger study might also show improvements in mortality rates.

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Original article

Vocal cord paralysis after subtotal oesophagectomy

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Background: Although vocal cord paralysis is a well known complication of subtotal oesophagectomy, precise data concerning origin, incidence and associated morbidity are lacking.

Methods: A retrospective study was performed of 241 patients who underwent transhiatal oesophagectomy for carcinoma of the mid/distal oesophagus between 1994 and 1998. Preoperative and postoperative laryngoscopy results were available for 140 patients.

Results: There were 109 men and 31 women, of mean age 63 years. Thirty-one patients (22 per cent) with recurrent laryngeal nerve paralysis were identified, three with bilateral and 28 with unilateral dysfunction. Paralysis occurred ipsilateral to the side of the cervical incision in 22 of 28 patients. It was permanent in six patients. The associated morbidity was substantial: pulmonary complications were more common in patients with vocal cord paralysis (12 of 31 *versus* 26 (24 per cent) of 109), leading to significantly more reintubations, and a significantly prolonged ventilation time and stay in the intensive care unit.

Conclusion: Although mostly transient, vocal cord paralysis is a frequent complication with significant associated morbidity. In an extended transthoracic resection (including a lymphadenectomy in the aortopulmonary window where the left recurrent laryngeal nerve is at risk) the cervical anastomosis should be made on the left side, to minimize the risk of bilateral vocal cord paralysis.

Paper accepted 12 September 1999

British Journal of Surgery 1999, 86, 1583–1586

Introduction

Vocal cord paralysis is a frequent complication of subtotal oesophagectomy. An incidence of up to 20 per cent has been reported[1–4]. Paralysis may be unilateral or bilateral and is the result of damage to the recurrent laryngeal nerve(s), leading to disorders of speech (almost all patients suffer from hoarseness), coughing, swallowing and breathing. Most paralysis is transient. Although transient hoarseness is not itself very troublesome, vocal cord paralysis may be associated with significant morbidity due to secondary pulmonary complications.

In a subtotal oesophagectomy, the oesophagus is transected in the neck after which a cervical anastomosis is performed. This is done in some three-stage operations and during all transhiatal procedures. The oesophagus is dissected circumferentially, which puts the recurrent nerves both on the ipsilateral and contralateral sides of the incision at risk. The thoracic part of the left recurrent nerve may also be injured during the thoracic phase of an extended transthoracic resection, especially while dissecting the lymph nodes in the aortopulmonary window and/or the left paratracheal lymph nodes.

In this institution the cervical anastomosis is performed on the right side during transhiatal oesophagectomy owing to the position of the patient. A left-sided anastomosis is preferred when an extended transthoracic approach is used, to minimize the risk of bilateral vocal cord paralysis. This strategy rests on the assumption that the ipsilateral recurrent nerve is more frequently damaged than the contralateral nerve in the cervical phase. To test this hypothesis and to analyse the morbidity associated with vocal cord paralysis after transhiatal oesophagectomy, a retrospective study was performed.

Patients and methods

Between 1994 and 1998, 241 patients had a subtotal transhiatal oesophagectomy for carcinoma of the mid/distal oesophagus. Some 140 of these 241 patients had results available of indirect laryngoscopy performed both before and within 2 weeks after the operation. There were

109 men and 31 women with a mean age of 63 (range 37–84) years. When vocal cord paralysis was diagnosed after operation follow-up was performed by an otolaryngologist. No distinction was made between paralysis and paresis, as this is hardly possible by indirect laryngoscopy. Vocal cord paralysis was therefore defined as an absence of movement or a decreased mobility (on indirect laryngoscopy) of one or both vocal cords on phonation compared with the preoperative examination. Permanent paralysis was defined as paralysis lasting more than 6 months.

Operative procedure

For a transhiatal procedure the patient is positioned in such a way that an urgent thoracotomy is possible without repositioning and redraping. This includes positioning of the patient in the dorsal decubitus position on a vacuum mattress moulded so that the table can be tilted 45° to the left without the patient sliding off. The right arm is draped and positioned along the side of the body and can be brought up when needed. The patient's head is turned to the left, denying access to the left side of the neck. This position allows an anterior thoracotomy to be done in the supine position. This technique has been described elsewhere[5]. In all but one patient in the present series the cervical incision was therefore made on the right side of the neck.

After opening the hiatus the diaphragm is incised to facilitate intrathoracic mobilization of the oesophagus including the tumour and perioesophageal tissue up to the carina. No formal lymph node dissection is done. When the oesophagus has been mobilized a gastric tube is constructed. In the cervical phase of the operation the oesophagus is mobilized circumferentially and transected low in the neck. The ipsilateral recurrent laryngeal nerve is identified when possible. On the contralateral side the dissection is performed close to the oesophagus with the contralateral border in view whenever possible to minimize the risk of injury to the contralateral nerve. A vein stripper is then inserted from the proximal end and the normal oesophagus proximal to the tumour is extracted 'blindly' from the mediastinum. Both vagal nerves are transected at the level of the carina. An anastomosis is made either with a running suture or with a stapling device, according to the preference of the surgeon. All operations were performed by, or under the direct supervision of, two senior surgeons experienced in oesophageal cancer surgery.

Postoperative pulmonary complications included pneumonia (an infiltrate seen on the chest radiograph or the isolation of bacteria from sputum culture for which antimicrobial therapy was given), atelectasis (lobar collapse on chest radiography), pleural effusion (a collection of fluid between the visceral and parietal pleural surfaces requiring drainage) and pulmonary embolus (ventilation–perfusion mismatch on lung scintigraphy). Pneumothorax was considered mainly as an intraoperative complication and was therefore not included.

Statistical analysis

Statistical analysis was performed with the aid of the SPSS statistical package (SPSS, Chicago, Illinois, USA). Differences between the groups were calculated using analysis of variance, Student's *t* test, χ^2 test or Fisher's exact test as appropriate. $P < 0.05$ was considered significant.

Results

None of the patients had vocal cord dysfunction before the operation. There was no visible tumour infiltration of the recurrent laryngeal nerve; it was not sacrificed deliberately in any patient. Thirty-one (22 per cent) of the 140 patients suffered from vocal cord paralysis after operation. There were three bilateral and 28 unilateral paralyses. Of the unilateral paralyses, 21 were on the right side and seven were on the left. Most of the patients with unilateral paralysis presented with hoarseness; two patients with unilateral paralysis also suffered from inspiratory stridor. Four patients had no symptoms at all. In 22 of the 28 patients with a unilateral paralysis the vocal cord dysfunction occurred on the same side as the cervical incision. Two of the three patients with bilateral cord paralysis developed severe stridor after extubation and had to be reintubated; one of them aspirated before reintubation. The other patient was asymptomatic.

Six paralyses (4 per cent) were permanent. In the other patients most symptoms disappeared within 2–3 months. Three patients were lost to follow-up: one died within 6 months and the other two were transferred to another hospital from where no follow-up laryngoscopy results were available.

Vocal cord paralysis was associated with significant morbidity. Twenty-six (24 per cent) of the 109 patients without vocal cord dysfunction had pulmonary complications. Of the 28 patients with unilateral vocal cord paralysis, nine had one or more pulmonary complications, compared with all three patients with bilateral paralysis (*Table 1*). Patients with vocal cord dysfunction were significantly more likely to require reinsertion of an endotracheal tube after operation. Reintubation or tracheotomy for respiratory failure was necessary in six of 28 patients with unilateral and two of three with bilateral vocal cord paralysis, compared with only four (4 per cent) of the 109 patients with normal vocal cord function ($P = 0.001$). Of the two patients with bilateral cord palsy requiring reintubation,

Table 1 Incidence of pulmonary complications related to vocal cord paralysis after subtotal oesophagectomy

	None ($n=109$)	Unilateral ($n=28$)	Bilateral ($n=3$)	Total ($n=31$)	P*
Pulmonary complications	26	9	3	12	0·11
Pneumonia	16	5	2	7	0·29
Atelectasis	7	3	1	4	0·26
Pleural effusion	3	1	0	1	1
Pulmonary embolus	1	1	1	2	0·12
Reintubation/tracheotomy	4	6	2	8	0·001

*Total with paralysis *versus* no paralysis (χ^2 test)

Table 2 Duration of ventilation, intensive care unit stay and hospital stay after subtotal oesophagectomy

	Duration of ventilation (days)	ICU stay (days)	Hospital stay (days)
No vocal cord paralysis	2 (1–13)*	4 (1–19)*	20 (10–155)
Unilateral paralysis	5 (1–33)*	7 (1–33)*	25 (10–67)
Bilateral paralysis	9 (1–3)*	17 (7–22)*	35 (21–60)

Values are mean (range). ICU, intensive care unit. *$P < 0{\cdot}05$ (analysis of variance), no paralysis *versus* unilateral paralysis *versus* bilateral paralysis

one died as the result of a massive pulmonary embolus and the other underwent a formal tracheotomy; the cannula was removed without complications 2 months later. Duration of ventilation and intensive care unit (ICU) stay were significantly prolonged when vocal cord paralysis occurred (*Table 2*). This finding was attributed to the reintubations; when only patients who did not need reintubation were considered, there was no difference in duration of ventilation or ICU stay. Hospital stay was also prolonged in patients with vocal cord paralysis, but this did not reach statistical significance.

There was no surgeon-dependent difference. Supervised surgery performed by a trainee did not carry a higher risk of injury to the recurrent nerve.

Discussion

Vocal cord paralysis due to injury to the recurrent laryngeal nerve most often occurs ipsilateral to the side of the cervical incision. Although mostly transient, it is associated with significant morbidity. Cord paralysis is a well known complication of oesophagectomy and other major surgery in the cervical region, but seldom investigated. A previous study showed that clinical assessment of vocal cord paralysis is unreliable without indirect laryngoscopy[6]. These results are confirmed by the present study in which a significant number of patients without symptoms had vocal cord paralysis diagnosed only by laryngoscopy.

The recurrent laryngeal nerves run in the tracheo-oesophageal grooves on both sides of the neck. The right recurrent nerve turns around the subclavian artery before running cranially; the left runs into the chest, turns around the aortic arch and then runs up cranially. It is the main motor nerve of the larynx. The recurrent laryngeal nerve also gives off branches to the cricopharyngeus muscle, which forms the upper oesophageal sphincter and plays a pivotal role in swallowing. Swallowing, breathing, speaking and coughing are all impaired after damage to the recurrent laryngeal nerve. In the early postoperative period this can result in aspiration pneumonia, especially when reflux is certain to develop owing to delayed gastric emptying[7]. When bilateral paralysis occurs, both vocal cords assume a median position, often leading to asphyxia and necessitating urgent reintubation/tracheotomy.

A cervical anastomosis can be performed during three-stage (abdomino–thoraco–cervical) subtotal oesophageal resection, although the anastomosis can also be made in the chest. A cervical anastomosis has the advantage of diminishing the risk of mediastinitis in case of anastomotic leak, but it also puts the recurrent laryngeal nerve at risk during the cervical dissection[2,3]. Both the left and the right recurrent laryngeal nerves may be injured in the neck when dissecting the oesophagus circumferentially from the trachea and when performing the oesophagogastrostomy. When performing an extended transthoracic resection, including a formal lymph node dissection in the posterior mediastinum, the left recurrent laryngeal nerve may be injured at the level of the aortic arch during the dissection of lymph nodes in the aortopulmonary window or along the left paratracheal groove. The right recurrent laryngeal nerve is not at risk, as it turns around the subclavian artery and is therefore not in the operative field.

During transhiatal resection the anastomosis is always made in the neck, which may lead to local injury of the recurrent laryngeal nerve. It is also possible to injure the recurrent laryngeal nerves by traction during 'stripping' of the oesophagus. However, there is no direct surgical danger to the intrathoracic (left) recurrent nerve as is the case in an extended transthoracic procedure.

Most surgeons prefer the left side for the cervival approach after three-stage oesophagectomy. In the neck the oesophagus is situated slightly to the left. The recurrent laryngeal nerve runs more anteriorly, thus facilitating dissection. However, the thoracic duct may be damaged as it enters the jugular vein on the left side, an argument against a left-sided approach. In a transhiatal procedure in this unit, the cervical oesophagus is routinely approached from the right side.

Vocal cord dysfunction impairs coughing and thereby increases the risk of pulmonary complications such as pneumonia and atelectasis. Reintubation and/or formal tracheotomy may be necessary, leading to a prolonged stay in the ICU. This study showed that vocal cord paralysis occurred more often on the same side as the cervical incision (right), which made it likely that the injury occurred during the cervical phase and was not due to traction on the vagal nerve during 'stripping'. This is also supported by the finding of more vocal cord dysfunctions after transhiatal than after Lewis–Tanner procedures[2,3,8]. This has implications for the choice of the side of the cervical incision. To minimize the risk of bilateral vocal cord paralysis the anastomosis should be made at the left side of the neck during an extended transthoracic resection. This minimizes the risk to the right recurrent laryngeal nerve. When performing a transhiatal resection the cervical incision can be made on either side because there is no direct danger to the intrathoracic left recurrent laryngeal nerve.

A number of other methods to avoid recurrent laryngeal nerve injury have been described, including early transection of the vagal nerves during 'stripping' to prevent traction, and avoidance of retractors in the tracheo-oesophageal groove. The incidence of nerve damage decreases with experience, but in this and other studies[9] there was no disadvantage in having operations performed by a trainee. In three cases the cord palsy was not surprising as there were technical difficulties during the cervical dissection or early re-exploration. The recurrent laryngeal nerve was never transected consciously.

The incidence of cord paralysis in the present study (22 per cent) is in line with published values[1–4]. In this study, postoperative laryngoscopy results were available for only 140 of the 241 patients. A certain selection bias can therefore not be excluded. The patients who did not undergo postoperative laryngoscopy might include those without cord palsy symptoms. The presented incidence of vocal cord paralysis might therefore be an overestimation.

In only six patients (4 per cent) was the cord paralysis permanent, suggesting that the injury inflicted to the recurrent nerve was probably due to traction as opposed to transection. Persistent hoarseness from recurrent laryngeal nerve paralysis causes deterioration in quality of life[10]. With the introduction of three-field lymphadenectomy for oesophageal cancer (including an extended cervical lymph node dissection) a higher incidence of vocal cord paralysis may be expected[10–12].

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Live kidney donor assessment in the UK and Ireland

Letter 1

Sir

I read with interest the article by Lumsdaine *et al.* (*Br J Surg* 1999; **86**: 877–81) in which several interesting and alarming points were raised. I was surprised by the number of centres involved in the live renal donor programme, with 31 centres performing 165 live donor transplants in 1997. This translates to about five live renal transplants per centre annually. Although the benefits of live kidney transplant were established in the article, the relative outcome between live and cadaveric transplantation for individual centres was not stated. Should live kidney transplantation be concentrated in designated centres, which can demonstrate better outcome for both the donor and the recipient? This complex issue can only be answered by nationwide audit. As a live liver donor for my daughter, I have personal experience of donor assessment and was particularly impressed by the rigid guidelines in King's College Hospital[1], which remains the only centre in the UK performing living-related liver transplants. The guidelines were based on a protocol developed by the Chicago Transplant Group. As a consequence of the associated psychological, ethical and clinical implications for both donor and recipient, it is imperative that national guidelines are established to facilitate audit and future planning of resources for a successful live kidney transplant programme which would lead to an increased donor pool and decreased patient waiting times for transplantation.

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1 Baker A, Dhawan A, Devlin J, Mieli-Vergani G, O'Grady J, Williams R *et al.* Assessment of potential donors for living related liver transplantation. *Br J Surg* 1999; **86**: 200–5.

Letter 2

Sir

The study by Lumsdaine *et al.* reviewed the assessment criteria used for live donor transplantation in the UK and Ireland. Concern was expressed about the lack of a standardized protocol for assessment and follow-up of live kidney donors. While we share these concerns, we note the absence of psychological criteria in the assessment, despite recent data linking postsurgical stress, depression, disruption of family relationships and even suicide in donors if the organ recipients subsequently develop transplant complications such as rejection and graft failure[1–3].

There is evidence that the psychosocial well-being of the donor is directly linked to the outcome of the transplant recipient. Concern over the psychological impact on living kidney donors at the University of Minnesota led to donors being studied retrospectively to determine the quality of life after donation. They found that donors generally reverted to the quality of life before donation, but a significant number (16 per cent of 979 donors between 1 August 1984 and 31 December 1996) had a poor psychosocial outcome[1]. Psychologists at the University of Buenos Aires explored interpersonal factors that influenced outcome in living related kidney transplants. They assessed 154 recipients and their donors prospectively and found that the pairs who were flexible and responsive to the transplant process had significantly better outcomes than the relationships that remained static over time.

Our unit is developing standardized protocols to include pretransplant assessment as a baseline for post-transplant psychosocial intervention. The integration of mental health professionals in transplant teams will ensure that clinicians are sensitized to psychosocial symptoms of donors with timely treatment. Greater understanding of the donor–recipient relationship and development of effective psychotherapeutic techniques may ensure that recipients and donors experience a more positive outcome, independent of the transplant course.

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Saphenoperitoneal shunts for patients with intractable ascites associated with chronic liver disease

Sir

Vadeyar *et al.* (*Br J Surg* 1999; **86**: 882–5) err when they describe saphenoperitoneal shunting for intractable ascites as a new technique. Saphenoperitoneal shunting, performed in an essentially similar fashion, was described 13 years ago in South India in a series of four patients[1].

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Surgical implications of underestimation of adrenal tumour size by computed tomography

Sir

We read with interest the study by Lau *et al.* (*Br J Surg* 1999; **86**: 385–7) which showed a significant underestimation of adrenal tumours by computed tomography (CT). They attributed this finding partly to the fact that CT measures the transverse diameter whereas the adrenal tumours grow in the craniocaudal or sometimes oblique direction. CT with thin sections should, however, be able to give accuracy in the longitudinal diameter of adrenal tumours.

They suggested that magnetic resonance imaging (MRI) or spiral CT could be more accurate in estimating size. We conducted a study to look at the accuracy of CT and MRI in sizing adrenal lesions and found a statistically significant underestimation of actual size by both modalities. In contrast to the study by Lau *et al.*, underestimation was more for tumours larger than 3 cm. There was no significant difference between MRI and CT.

Whether spiral CT is superior to axial CT and MRI requires investigation. It would be interesting to ascertain whether MRI has any advantage over CT in making a more accurate diagnosis.

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Transhiatal approach to total gastrectomy for adenocarcinoma of the gastric cardia

Sir

Wayman *et al.* (*Br J Surg* 1999; **86**: 536–40) suggest that the 30 per cent incidence of positive proximal resection margins after total gastrectomy with Roux-en-Y reconstruction for carcinoma of the gastric cardia may be unavoidable because jejunal mobilization is limited. One can only speculate, therefore, how others have achieved an incomplete resection rate of only 11 per cent[1]. Wayman *et al.* followed their patients for a minimum of 12 months, but there were no survival data to support their suggestion that the prognosis of patients with positive resection margins is dependent on disease stage. In the 10-year period to December 1992, 250 patients underwent one-stage left thoracoabdominal oesophagogastrectomy with gastric tube reconstruction for cardia carcinoma in the Edinburgh cardiothoracic unit. Stage III and IV disease was present in 27 of 33 patients with positive resection margins (22 had positive proximal margins) and 168 (77 per cent) of 217 with clear margins. All patients were followed for at least 12 months. The median survival was 9·5 months for 32 hospital survivors with positive margins and 15 months for 204 survivors with clear margins. These data suggest that, for patients with similar disease stage, incomplete longitudinal clearance compromises survival. A recent study has demonstrated no positive proximal margins after two-stage left thoracoabdominal oesophagogastrectomy for carcinoma of the cardia[2]. In terms of achieving adequate longitudinal clearance, therefore, the operation practised by the Newcastle group may be suboptimal and the relative merits of the transhiatal over the left thoracoabdominal approach irrelevant.

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Authors' reply

Sir

The letter from Adams *et al.* demonstrates the considerable confusion regarding the definition of a cardia cancer and the most appropriate surgical approach for these tumours. We reported a transhiatal approach for total gastrectomy with Roux loop reconstruction for types 2 and 3 junctional adenocarcinoma[1] and do not perform this procedure for type 1 (lower oesophageal) junctional tumours. Positive proximal resection margins occurred in 20 per cent of the specimens from our first 20 transhiatal procedures, although it should be noted that the oesophageal staple donuts in these patients were all clear. In the 56 consecutive operations performed to date there were only five patients (9 per cent) with positive resection margins. Our 1-year survival rate is 86 per cent and all five patients with positive resection margins died from distant metastases at 9–22 months. The results from the Edinburgh cardiothoracic unit have not been published but are in stark contrast to those presented by the same group at the British Society of Gastroenterology in 1994[2]. Positive resection margins were found in nearly one-quarter of 344 patients undergoing oesophagectomy with gastric tube reconstruction via a left thoracolaparotomy and one can only speculate as to why over 50 per cent of their patients were dead within 12 months of surgery. The Edinburgh group appears to have both proximal and distal positive resection margins, which may reflect the limitations of the use of the stomach for reconstruction after a resection for proximal gastric cancer. While Anikin *et al.*[3] managed to achieve clear resection margins for a small select group of true cardia tumours employing a two-stage left-sided procedure, they report considerably higher morbidity and mortality than in our series. Their survival figures are as poor as those from the Edinburgh group, suggesting that either their patient selection is suboptimal or they are leaving behind malignant disease at sites other than the anastomosis.

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Modern management of pulmonary embolism

Sir

We read with interest the comprehensive review by Tai *et al.* (*Br J Surg* 1999; **86**: 853–68) on the management of pulmonary embolism. However, on the issue of pharmacoeconomics, simply comparing the costs of low molecular weight heparins (LMWHs) to that of unfractionated heparin (UFH) does not give a fair representation of the overall treatment costs. Anticoagulation with UFH requires laboratory monitoring, increased nursing time in its administration, more medical disposables and the related issue of achieving a therapeutic APTT which can extend hospital stay, all of which adds to the cost of treatment with UFH but not to that of LMWH therapy.

Hoffmeyer *et al.*[1] evaluated the cost implications of using tinzaparin or intravenous UFH in the treatment of acute pulmonary embolism from the clinical trial published by Simonneau *et al.*[2]. The cost per patient, including initial treatment and cost of managing adverse outcomes, was found to be £191·81 for patients receiving UFH and £186·64 for patients treated with tinzaparin. Excluding the costs of managing adverse outcomes, the cost of treating with UFH was still considerably greater at £136·70 per patient as opposed to £120·22 in the tinzaparin treated group. Hence, use of tinzaparin can result in overall cost saving in spite of the individual drug cost being greater, an issue of increasing prominence in the cost-conscious health systems of today.

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Authors' reply

Sir

We thank Messrs Aldwinckle and Timmis for their comments. With reference to the paper by Hoffmeyer *et al.*[1], we wish to make the following points. (1) The paper is a model analysis based on a series of assumptions. (2) Hoffmeyer *et al.* did not use prospectively gathered data, but relied on the opinions, obtained by interview, of eight clinicians (details of interview protocol were not published). (3) The trial by Simonneau *et al.*[2], used as a source of outcome data, was conducted in France, Belgium and Switzerland, yet the cost implications are discussed in the context of UK practice. (4) The sensitivity analysis, when looking at total expected costs for both treatments, comments 'The drug chosen has a relatively small impact on total costs, which are largely driven by e.g. the costs of hospital stay'. (5) The study was performed by economic consultants as part of a programme funded by Leo Pharmaceuticals; a relevant fact not referred to by Messrs Aldwinckle and Timmis.

Our review points out that the unit cost of LMWHs is higher than UFHs and that 'LMWHs offer the benefit of simple administration without the need for vigilance in monitoring'.

Costs of drugs to individual hospitals and the costs of monitoring vary widely across the National Health Service in the UK; the most relevant economic analysis is performed by hospitals on the basis of local costs. Our review would be a good starting point when considering such an analysis.

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2 Simonneau G, Herve S, Charbonnier B, Page Y, Laaban JP, Azarian R *et al.* A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997; **337**: 663–9.

Corrigendum

G. D. Treharne, M. M. Thompson, M. S. Whiteley, P. R. F. Bell. Physiological comparison of open and endovascular aneurysm repair. *Br J Surg* 1999; **86**: 1483 (Letter).

The correct version of *Table 1* is as follows:

Table 1 Mortality rates for conventional AAA repair according to P–POSSUM score (overall mortality 16·3 per cent)

Physiological score	No. of patients	Mortality rate (%)
0–15	0 of 18	0
16–20	4 of 41	10
21–25	7 of 27	26
>25	6 of 15	40

The author apologizes for the errors.

Last's Anatomy. Regional and Applied. 10th ed.

C. S. Sinnatamby

246 × 187 mm. Pp 539 Illustrated 1999 Edinburgh. Churchill Livingstone £35

Last's Anatomy contains a massive amount of clinically orientated anatomy but, unlike some anatomy reference texts, is not too large or cumbersome for routine use. In this edition, the text is made even more clinically relevant and detailed anatomy has been omitted. Examples of the increasing clinical relevance are the inclusion of surface anatomy and radiographs. The illustrations are appropriate and of a high standard. This represents an excellent text for undergraduate students (of medicine and related professions), surgical trainees and practising surgeons.

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Operative Strategies in Inflammatory Bowel Disease

F. Michelassi and J. W. Milsom (eds)

284 × 218 mm. Pp. 515. Illustrated 1999. New York Springer £114·50.

The complexity of management of inflammatory bowel disease, because of its clinical diversity, is soon realized by those in this field. The editors are well versed in the pitfalls in surgical practice, and appropriately dwell on many problematic and contentious areas with a comprehensive and authoritative approach. This fulfils an essential educational objective. The first section is an update on current understanding. The present advances in pathogenesis, the aetiology and the epidemiology, although complementary, do not have particular relevance to the theme of the book. The chapters on surgical pathology, endoscopy and radiology are especially informative and layout clearly the basic and practical fundamentals that influence management. The advent of novel therapies was worth including, being part of the treatment armament. Subsequent sections address the operative options and techniques for the many varied eventualities encountered when providing pathways of management, a different approach from didactic textbooks. The contents and style of presentation are of high quality, reflecting the experience of the contributors. The book is enjoyable to read, well written and is liberal with illustrations and references. It is a commendable reference that broadly defines the knowledge base for the surgical trainee and is a reliable reference for the specialist surgeon. It deserves a place in every surgical library.

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Incontinence

M. Lucas, S. Emery and J. Beynon (eds)

250 × 175 mm Pp. 305. Illustrated 1999 Oxford: Blackwell Science £69·50

This is an interesting book that is different from other textbooks in that it combines the views of urologists, gynaecologists and colorectal surgeons. For surgeons, it is good to see what urologists and gynaecologists can do in diagnosis and therapy. However, the pages on faecal incontinence are limited. This limited detail of bowel problems is probably enough for urologists and gynaecologists, but it is insufficient for surgical trainees or specialists who wish to develop an incontinence practice, as mentioned in the preface. While it is true that urinary incontinence is a commoner problem than fecal incontinence, a representation of only approximately 40 pages out of 300 undervalues the importance of fecal incontinence; even more striking is the bibliography in which only nine references out of 150 deal with the subject. The chapters on psychological aspects in urinary incontinence, economics and development of an integrated continence care are of general interest and, for all non-surgical aspects, this book deserves the attention of surgeons. The message of cooperation with other specialists and integration of continence care is valuable, but it would be even better with a more even input from all specialists.

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Video-Assisted Thoracic Surgery

W. S. Walker (ed.)

281 × 223 mm Pp 232 Illustrated. 1999. Oxford Isis Medical Media. £95.

It gives me great pleasure to review this unique book. It is well structured, and the complexity of the procedures unfold with clarity of language and excellent diagrams. The different contributors take the reader through the various stages of the operations, highlighting the key points in well organized tables. The endoscopic pictures and anatomical diagrams are of the highest standard. Particularly useful to the reader are the tables in which major points, considered important by the editor, are summarized for each chapter. This book is, without doubt, a comprehensive effort in bringing together the knowledge and skills of some of the most prestigious names in the world of video-assisted thoracic surgery. In my opinion, it is the most complete collection of knowledge in this sphere to date. I have no hesitation in recommending this volume to anyone wishing to have an in-depth knowledge of this particular subspecialty in thoracic surgery, as well as to the practising, experienced thoracic surgeon.

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Bladder Cancer. Biology, Diagnosis and Management

K. N. Syrigos and D. G. Skinner (eds)

250 × 190 mm Pp 469. Illustrated 1999. Oxford Oxford University Press £79·50

Advances in urology are currently occurring at a rapid rate both clinically and in basic science. This book, approximately equally divided between these two areas, makes a very good attempt to keep abreast of these changes. For a textbook of this type, the references are up to date; the page layout is particularly pleasing with ample margins for adding annotations to the text. Most chapters conclude with a key points box. While some of these are good, most fail, which is hardly surprising as it is impossible to summarize often 20 or more pages of in-depth material in just a few lines without appearing superficial. However, this is a minor point that does not detract from a book that is generally easy to read. My most serious criticism is the amount of repetition between chapters. While this may be hard to edit in the context of a multiauthor book, there are several vast areas that are repeated. Although this means that each chapter, read in isolation, can stand alone, it becomes irritating when reading large sections of the volume. Accepting this fault, this book should enhance the level of the reader's knowledge, in a fairly painless way, from that which can be obtained from a general textbook to a more specialist level.

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Immunosuppression in Transplantation

L. C. Ginns, A. B. Cosimi and P. J. Morris (eds)

286 × 220 mm Pp. 140 Illustrated 1999 Boston, Massachusetts: Blackwell Science £69 50

This relatively slim volume provides a multiauthor reference manual that covers all aspects of transplant immunosuppression strategy, past, present and, perhaps, future. The text is unbalanced, with a very short chapter on azathioprine (which has been used in many thousands of successful transplant recipients over 30 years), and a long chapter on mycophenolate mofetil (which underwent clinical studies in 1991 and, despite its efficacy, is struggling to find a firm place in the UK because cost may outweigh the benefit). The chapter on cyclosporin is particularly heavy-going and may appeal to a chemist or pharmacologist; it contains little on the huge volume of experimental animal work that went on in the 1980s. By contrast, the chapter on mycophenolate mofetil is full of experimental animal detail. Substantial parts of a section on new small molecule immunosuppressants covers much information that is present in better detail elsewhere in the text. Chapters on the role of steroids and biological immunosuppression are, by contrast, excellent and readable by all those interested in clinical transplantation.

Better cohesion by the editors should have reduced duplication and ensured a more uniform format. I cannot agree with their preface that this volume will be useful to the wide variety of health professionals associated with clinical transplantation. Transplant-related thesis writers may find some of the reference material of value.

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Scientific Surgery

Alback A, Kantonen I, Ihlberg L, Lepantalo M. Valvulotomy of non-reversed saphenous vein bypass grafts: a randomised, blinded, angioscopy-controlled study. *Eur J Vasc Endovasc Surg* 1999; **18**: 144–8.

Two different valvutomes were compared, there was no significant difference in the number of vein valve cusps correctly lysed (69 per cent with the plastic disposable device *versus* 78 per cent with the metal valvutome)

Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K *et al* and the Gastric Cancer Surgical Study Group. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa negative gastric cancer: a randomised trial. *Lancet* 1999; **354**: 273–7.

This study included 579 patients, 5-year survival rate was not improved by adjuvant chemotherapy (85·8 *versus* 82·9 per cent in controls)

Dath D, Park AE. Randomized controlled trial of bupivacaine injection to decrease pain after laparoscopic cholecystectomy. *Can J Surg* 1999; **42**: 284–8.

Ninety-seven patients were included; mean postoperative pain scores were reduced by bupivacaine after 2 and 6, but not 10 h. More patients who had bupivacaine chose to go home on the day of operation (66 *versus* 43 per cent, *P* = 0·034)

The MRC Laparoscopic Groin Hernia Trial Group. Laparoscopic *versus* open repair of groin hernia: a randomised comparison. *Lancet* 1999; **354**: 185–90.

A total of 928 patients were included. Laparoscopic repair was associated with fewer wound complications, earlier return to work and less late pain, however, all three serious complications occurred after laparoscopy, as did all seven recurrences

Bellantone R, Bossola M, Carriero C, Malerba M, Nucera P, Ratto C *et al.* Structured *versus* long chain triglycerides: a safety, tolerance and efficacy randomized study in colorectal surgical patients. *J Parent Ent Nutrition* 1999; **23**: 123–7.

Nineteen patients were randomized to receive structured or long chain triglycerides as the energy source during parenteral nutrition. Triglyceride levels and nitrogen balance were similar without any reported adverse effects

Valverde A, Hay J-M, Fingerhut A, Boudet M-J, Petroni R, Pouliquen X *et al.* Senna *versus* polyethylene glycol for mechanical preparation the evening before elective colonic or rectal resection. a multicenter controlled trial. *Arch Surg* 1999, **134**: 514–18.

A total of 523 patients were included from 18 centres. Senna produced a more effective preparation and was better tolerated, although the type of preparation did not influence outcome

Merad F, Hay JM, Fingerhut A, Yahchouchi E, Laborde Y, Pelissier E *et al.* Is prophylactic pelvic drainage useful after elective rectal or anal anastomosis? A multicenter controlled randomized trial. *Surgery* 1999; **125**: 529–35.

Some 494 patients were randomized, there was no significant difference in anastomotic leak rate (total 6·3 per cent) or death (3·2 per cent drain *versus* 4 per cent no drain)

Kelly MD, King J, Cherian M, Dwerryhouse SJ, Finlay IG, Adams WJ *et al.* Randomised trial of preoperative cimetidine in patients with colorectal carcinoma with quantitative assessment of tumour-associated lymphocytes. *Cancer* 1999; **85**: 1658–63.

Some 125 patients were randomized to either 5 days of cimetidine before operation or a control group. There was a trend towards improved survival with cimetidine, possibly as a result of increased lymphocytic infiltration around the tumour.

Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five year results of a randomized trial. *J Vasc Surg* 1999; **29**: 589–92.

One hundred patients (133 legs) were included. Routine stripping reduced the reöperation rate at 5 years from 12 of 58 to three of 52 (relative risk 0·28, 95 per cent confidence interval 0·13–0·59, *P* = 0·02)

Chung RS, Rowland DY, Li P, Diaz J. A meta-analysis of randomised controlled trials of laparoscopic *versus* conventional appendectomy. *Am J Surg* 1999; **177**: 250–6.

Seventeen trials including 1962 patients were assessed. Modest but statistically significant advantages were found in postoperative pain and wound infection, and recovery, although the operation took longer.

Robinson BI, Fletcher JP, Tomlinson P, Allen RDM, Hazelton SJ, Richardson AJ *et al.* A prospective randomised multicenter comparison of expanded polytetrafluoroethylene and gelatin-sealed knitted Dacron grafts for femoropopliteal bypass. *Cardiovasc Surg* 1999, **7**: 214–18.

Some 108 patients were included, most having above-knee bypass. There was no difference in patency after 3 years: 52 per cent with polytetrafluoroethylene and 47 per cent with Dacron

Argawala SS, Ferri W, Gooding W, Kirkwood JM. A phase III randomised trial of dacarbazine and carboplatin with and without tamoxifen in the treatment of patients with metastatic melanoma. *Cancer* 1999; **85**: 1979–84.

Addition of tamoxifen did not improve survival in the 56 patients studied. Median survival was 4·6 months with tamoxifen and 7 months without

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This must not exceed 200 words and should be presented in a structured format. **Background:** state why the study was done and its main aim. **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings including important numerical values. **Conclusion:** state the main conclusions but controversial or unexpected observations may be highlighted.

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References

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In the text, number references consecutively by superscript:^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence.

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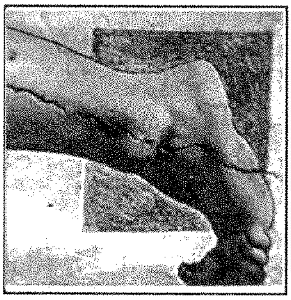

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